# I. Completion of a Total Synthesis of Peloruside A. II. Studies toward the Total Synthesis of Spiro-Prorocentrimine

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# I. Completion of a Total Synthesis of Peloruside A

# II. Studies Toward the Total Synthesis of Spiro-prorocentrimine

## *Abstract*

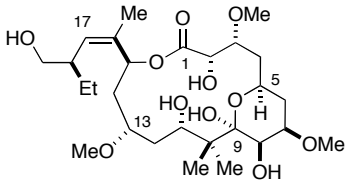
### I. Completion of a Total Synthesis of Peloruside A

The completion of a 22 step synthesis of the marine natural product peloruside A is presented. The second generation strategy cuts 10 steps from longest linear sequence of the Evans group's first generation synthesis of peloruside A by changing the order of fragment coupling operations and maintaining $C_1$ and $C_9$ at their final oxidation states over the course of most of the synthesis. Key steps include two highly diastereoselective aldol fragment couplings, a tin tetrachloride mediated hydrosilylation and a macrolactonization on a seco acid containing no cyclic templating elements.

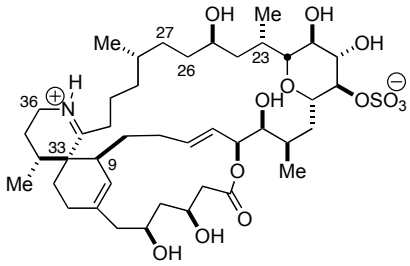
### II. Studies Toward the Total Synthesis of Spiro-prorocentrimine

The development of an intermolecular Diels–Alder approach toward the marine natural product spiro–prorocentrimine is described. This work began with the adaptation of the Evans group's previous intramolecular Diels–Alder approach. It was found that protonated imines bearing non-coordinating counterions were of sufficient reactivity to allow cycloaddition to occur even on dienes that were unreactive under the previous best conditions. In the course of these studies, isomerization of a macrocyclic diene during the course of a Diels–Alder reaction complicated the stereochemical outcome of the reaction. Reaction conditions to suppress the isomerization and obtain Diels–Alder adducts bearing the correct configuration at both $C_9$ and $C_{33}$ were developed based on a qualitative consideration of the pKas of species present in the reaction. The intrinsic facial selectivity

of several macrocyclic dienes was examined to help explain the course of the Diels–Alder reaction. Other key steps include an iron catalyzed olefin formation, the highly diastereoselective hydrogenation of a trisubstituted olefin in the presence of an enol ether, protecting group studies to suppress the contraction of a 15 membered lactone to a 6 membered lactone and studies of a protecting group strategy to allow installation of a sulfate. Lessons learned from this work and previous efforts are combined in a proposal for a bioinspired synthesis of spiro-prorocentrimine with a longest linear sequence of less than 30 steps.




Peloruside A




Spiro-prorocentrimine

## *Acknowledgements*

I want to thank David Evans for taking me into his group and giving me the chance to be part of "the Evans School". Dave was the reason I applied to Harvard, and I am glad I was able to work for him despite the round-about way of getting there. When I initially joined Dave's group, he introduced me to the term "Grubstake". I like to feel that my chemical prospecting gave a decent return on the initial investment. Dave gave me the opportunity to work on two very different projects, which I like to think doubled my learning opportunities. Thanks also for giving me complete freedom to explore my interest in organometallic chemistry (and even main group chemistry) in the context of our work. Who ever would have thought polyketides could withstand tin tetrachloride? I would like to thank Eric Jacobsen and Matt Shair for being on my committee and taking an interest in my progress during my studies. Matt's helpful career advice is much appreciated. I also owe a debt of gratitude to Dieter Seebach, who was a strong advocate for me when I needed it the most.

It seems reasonable that the impact people have had on one's life will be inversely proportional to the age at which they first became part of one's life, and proportional to the length of time they were in it. It therefore seems logical that I owe the most to my parents, Marjorie and William Speed, and my grandmother Muriel Harrison. Together you created a wonderful home for me to grow up in, and you all had a part to play in teaching me about the joys of living, and knowing. In preparing earlier, and very lengthy drafts of this acknowledgement, I came to the realization that I should maybe just stick to the chemistry. So much will therefore go unsaid here, but rest assured it is not unfelt. I had a fantastic upbringing in Liverpool Nova Scotia, and I have my family, many friends, teachers, church and community members to thank for that. I wouldn't change a thing. A more recent addition to my family is my stepfather Luke Powell, and my stepsisters

Emma and Annie, and I thank them for all of their support and advice throughout my time in grad school, especially in my difficult second year. Travelling home for Christmas in the blizzard of 2007 will always be memorable. Germane to the subject at hand, I would like to thank Richard Dumeah for being a fantastic high school chemistry teacher, and entirely representative of the fantastic quality of all of the teachers I was blessed to have at Liverpool Regional High School. You taught me to not be complacent, and you have a fearsome track record in producing great chemists. On that note, thanks to Ian Young for being such a great role model, and helping to steer me into a subject I have enjoyed so much. An enormous influence in my undergrad years and beyond was Craig Stamp. All the best parts of how I try to think about mechanism and recognize patterns and be creative come from your patient tutelage. You were the first one who got me thinking critically and showed me what it means to really stick to your principles, and while that has gotten me in some sticky situations from time to time, I think it must all be for the best in the long run. I owe a lot to Dr. Pincock and Dr. Burnell for agreeing to take me into their laboratories as a green undergrad and giving me very interesting problems to work on. Dr. Pincock introduced me first hand to many of the techniques, reactions and mechanistic thought I still use today. I was able to hone these skills in the Burnell lab, and I want to thank Craig, Liang Zhao, Paul Thornton, Fuye Gao, Jeremy Hughes and Ian Pottie for being such great friends and making such a great work environment. Dr. Burnell has especially gone out of his way to give me a great deal of career and life advice, and for that I am thankful. I was also fortunate to have had many good friends (including some from all the way back to elementary school) to make the time in Halifax more pleasant. Thanks Ian, Brad, Rebecca, Mark, Malcolm, Ericka, Lise, Adam, Matt, Dave, J.R., Darcie, Sam, Dina, Ivan, Jennifer, Graeme, Jacklyn, Jacob, Luke, Paige, Meghann, and many more as well.

My co-worker in the start of my time in the Evans group was Dr. Dennie Welch, and I could not have had a better experience. I joined a project that was very well underway, but Dennie welcomed me and entrusted me with some key transformations. His patient teaching and explanation of the subtleties of the aldol reaction made for a very smooth introduction to the group. Thanks for being such a great teacher. My co-worker on the spiro-prorocentrimine project was Dr. Pascal Bindschädler. I always enjoyed Pascal's optimism and enthusiasm. His expertise in protecting group chemistry, which was gleaned from his work with carbohydrates was an excellent addition to our project. I still got to do the only carbohydrate work in our route. Bring on the 10 L sep funnel filled with DCM. I also want to thank Pascal for being so patient with me and my fickle ideas during our long exploration of various alkylated and acylated iminiums that ultimately led to dead end after dead end. Pascal's experience taught me what virtues patience and optimism can be in the lab. Dr. David Marcoux was an honourary member of the spiro-prorocentrimine project, and an expert in the reactivity of iminium ions. Thanks for being there to bounce ideas off of, and for the fruitful collaboration we had comparing reactivity of the 6 and 7 membered ring cases. Marcoux is also a fellow citizen of the great white north, so it was nice to have a friend to get some advice and knowledge from on how academia beyond the bachelor's degree works back home. Even though I did not overlap with them on the project, I also must especially thank Dr. George Borg for making the all important macrocycles, Dr. Joe Pero for figuring out how to get them to react, Dr. Martin Juhl for his many contributions to the pyran and hydrogenation chemistry, and Dr. Anna Chiu for starting the whole iminium business. Mr. Stephen Ho, Dr. George Moniz and Dr. Andreas Reichelt are all thanked for their contributions to the Peloruside project. I have been fortunate to have many talented coworkers and friends over most of my time here. I want to thank especially my lab mates from the Evans lab. I overlapped with about 30 people during my time here, so I won't thank you all here, but those of you that overlapped with me the longest are thanked the most. Thanks to Joe

Wzorek, Jason Beiger and Art Catino, Eugene Kwan, Drew Adams, Pete Fuller, Paulo Vital, Tom Vargo, David Marcoux, Simone Bonazzi, Egi Kattnig, Pascal Bindschädler, Dennie Welch, Andrew Weiss and the rest of you all for being my closest social circle, for helping me keep sane, and for many engaging and inspiring conversations about chemistry, economics, politics, the politics of science, electricity and the world at large. We had a lot of great times both inside and outside of lab, and I believe I almost broke even at poker. At various times, Border Café, Thursdays at Cambridge Common, Saturday Boca then Qdoba runs, Wiffle Ball, top 5 lunches, blaring dance music, slow clapping at secret meetings and Tetris cheering marathons have all been institutions in our lab, and will be missed. Joe and Jason, my classmates have long suffered my idiosyncracies and I was truly blessed to have such great friends as well as co-workers during grad school. Thanks also to Eugene and Art who have also put up with me just as long, and have been great friends and provided much fruitful conversation.

Outside the lab, the fine dining that Cambridge had to offer was a welcome respite. I want to thank Grace for frequent lunch sessions that generally involved a lot of optimism and a wide range of interesting topics. A nice environment was found in the lab right below mine, and I want to thank Tejia, Whitney, Edwin, Yui, Marvin, Anna, and Amanda and all the various other Friday dinner folks for the great conversations we had. Thanks to the folks from the Shair, Jacobsen, Myers, Liu, and Corey labs, and the folks in the back bay, to mind comes: Brain, Ben, Amy, Naomi, Cheyenne, Corinna, Dave, Jim, Adam, Andy, Noah, Alec, Qiu, Kevin, Ryan, Sarah, Theresa, Megan, Rob, Kristine, Rebecca, Dave, Charles, and Jean, for all of your chats at happy hour, help with chemistry and finding chemicals, TFing and general good cheer that makes the department a more pleasant place.

Friendships in Boston did not stop at Harvard. I want to thank Heather, Matt, Vanessa, Rylan, Laura, Alison, Vlad, Lindsay, Krissy, Derek, April, Stephen, and Andrew, who in various combinations joined me for beer, griping, Red Sox games, hiking, trips to Canada and even a trip to Europe. Apologies, as I am sure I have omitted some names that deserved to be in here, I will cry pardon over a beer.

*Dedicated to my mother Marjorie Speed Powell and*

*to the loving memory of William Speed and Muriel Harrison. Thanks for everything.*

## *Table of Contents*

## *List of Abbreviations*

| | |
|---|---|
| AB | AB spin system (Pople Notation) |
| acac | acetylacetonate |
| ap. | apparent |
| aq. | aqueous |
| Ar | aromatic (generic) |
| atm | atmosphere |
| BAIB | bis-acetoxyiodobenzene |
| $BAr^F$ | tetrakis(3,5-trifluoromethylphenyl)borate |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| $Boc_2O$ | di-*tert*-butyldicarbonate |
| box | bisoxazoline |
| br. s | broad singlet |
| Bu | butyl |
| Bz | benzoyl |
| *c* | concentration (g/100 mL) |
| CBS | Corey- Bakshi- Shibata |
| COD | 1,4- cyclooctadiene |
| COSY | Correlation spectroscopy |
| Cp | cyclopentadienyl |
| CSA | camphorsulfonic acid |
| *d* | deutero |
| d | doublet |
| DCE | 1,2-dichloroethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |

| | |
|---|---|
| DIBAL-H | di-*iso*-butylaluminum hydride |
| DIPEA | di-*iso*-propylethylamine (Hünig's base) |
| DMAP | 4-(*N,N*-dimethylamino)pyridine |
| DMBM | (3,4-dimethoxy)benzyloxy methyl |
| DMDO | dimethyldioxirane |
| DME | dimethoxyethane |
| DMF | dimethylformamide |
| DMP | Dess- Martin Periodinane |
| DMPU | N, N'-dimethylpropyleneurea |
| DMS | dimethylsulfide |
| DMSO | dimethylsulfoxide |
| dr | diastereomeric ratio |
| *E* | entgegen |
| *ee* | enantiomeric excess |
| ESI | electrospray ionization |
| Et | ethyl |
| g | gram(s) |
| *gem* | geminal |
| h | hour(s) |
| HFIP | hexafluoroisopropanol |
| HKR | hydrolytic kinetic resolution |
| HMDS | hexamethyldisilazane |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| Im | imidazole |
| IR | infrared spectroscopy |

| | |
|---|---|
| *J* | coupling constant |
| KHMDS | potassium hexamethyldisilazide |
| $LD_{99}$ | concentration that will kill 99% of a given animal population when administered as a single dose |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium hexamethyldisilazide |
| Lut | 2,6 lutidine |
| *m* | meta |
| m | multiplet |
| M | molar (moles/liter) |
| *m/z* | mass to charge ratio |
| m-CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| min | minute(s) |
| mL | milliliter(s) |
| mol | mole(s) |
| MOM | methoxymethyl |
| MS | Mass Spectrometry |
| Ms | methanesulfonyl |
| NBD | norbornadiene |
| NaHMDS | sodium hexamethyldisilazide |
| NMO | N-methylmorpholine-N-oxide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| *o* | ortho |
| ºC | degrees Celsius |
| OTf | trifluoromethanesulfonyl |

| | |
|---|---|
| *p* | para |
| Pd/C | palladium on carbon |
| Ph | phenyl |
| PMB | (4-methoxy)benzyl |
| PMBM | (4-methoxy)benzyloxy methyl |
| ppm | parts per million |
| PPTS | pyridinium *para*- toluenesulfonate |
| psig | pound-force per square inch (gauge) |
| PTAD | 4-phenyl-1,2,4-triazoline-3,5-dione |
| py | pyridine |
| *R* | rectus (Cahn- Ingold- Prelog system) |
| R | alkyl group (generic) |
| $R_f$ | retention factor |
| ROESY | Rotating frame Overhauser effect spectroscopy |
| rt | room temperature |
| *S* | sinister (Cahn-Ingold-Prelog system) |
| s | singlet |
| t | triplet |
| *t* | tertiary |
| TAS-F | tris(dimethylamino)sulfur(trimethylsilyl)difluoride |
| TBAF | tetra(*n*-butyl)ammonium fluoride |
| TBAI | tetra(*n*-butyl)ammonium iodide |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |

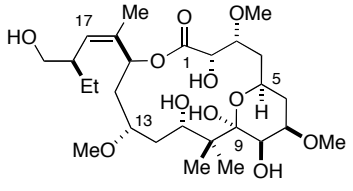
| | |
|---|---|
| TFT | α,α,α-trifluorotoluene |
| THF | tetrahydrofuran |
| TIPS | tri-*iso*-propylsilyl |
| TLC | thin layer chromatography |
| TOCSY | total correlation spectroscopy |
| TON | Turnover number |
| TMS | tetramethylsilyl |
| Ts | *para*-toluenesulfonyl |
| *vic.* | vicinal |
| q | quartet |
| quant. | quantitative |
| *Z* | zusammen |
| δ | chemical shift (parts per million) |

# *Chapter 1*

## Introduction to Peloruside A[1,2]

### I. Isolation of Peloruside A

The structure of peloruside A (**1**) was disclosed by Northcote and coworkers in 2000 (Figure 1.1).[3] Peloruside A was obtained from specimens of *Mycale hentscheli* sponges in the Pelorus Sound on the South Island of New Zealand. The initial isolation yielded 3 mg of peloruside A from 170g wet weight of sponge. Only samples of sponge collected at the deeper range at which the sponge species grew contained peloruside A. Peloruside A contains a 16 membered macrocyclic lactone, with an embedded tetrahydropyran. The structure is highly oxygenated. Other features of interest include geminal dimethylation at $C_{10}$ and a *Z* olefin at $C_{16}$–$C_{17}$. The structure of peloruside A was determined by extensive $^1$H NMR studies. The numbering shown in the figure below is used to describe the various fragment couplings in the remainder of this chapter.




(+)-Peloruside A
**1**

**Figure 1.1** The structure and absolute configuration of peloruside A.

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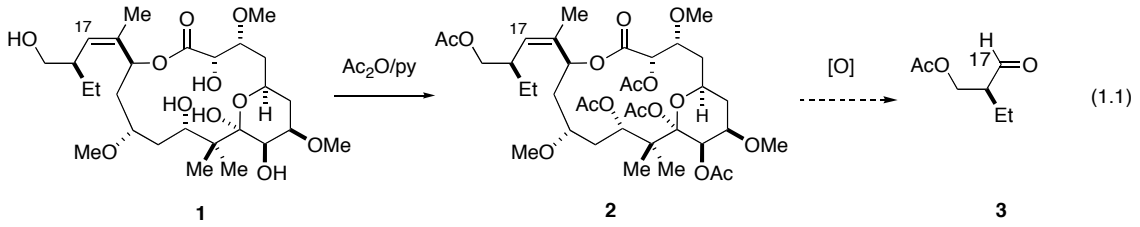
(1) Reproduced in part with permission from Evans, D. A.; Welch, D. S.; Speed, A. W. H.; Moniz, G. A.; Reichelt, A.; Ho, S. "An Aldol-Based Synthesis of (+)-Peloruside A, A Potent Microtuble Stabilizing Agent" *J. Am. Chem. Soc.* **2009**, *131*, 3840-3841. © 2009 by The American Chemical Society.

(2)Work conducted by my coworker Dr. Dennie Welch, and work conducted by my predecessors Dr. George Moniz and Dr. Andreas Reichelt is summarized within this chapter.

(3) West, L. M., Northcote, P. T., Battershill, C. N. *J. Org. Chem*. **2000**, *65*, 445-449.

Workers at Northcote's institution had attempted to determine the absolute configuration of peloruside A by chiral GC analysis of the products of an ozonolytic or dihydroxylation/ lead tetracetatate cleavage of the alkene in **2**, derived from the peracetylation of peloruside A (Equation 1.1). Unfortunately neither set of conditions resulted in any compound with a GC retention time equivalent to either enantiomer of an authentic racemic sample of **3** on a chiral column. This failure was attributed to the sensitivity of aldehyde **3** to oxidative conditions and the small scale on which the reaction was attempted (0.25 mg).[4]




1 2 3 (1.1)

The absolute configuration of (+)–peloruside A was therefore not known at the time of Northcote's initial disclosure. The assigned structure was confirmed and the absolute configuration was determined with the completion of the first total synthesis by De Brabander and co-workers in 2003.[5] De Brabander synthesized (-)–peloruside A, meaning that the initial structure drawn by Northcote and the initial synthesis by De Brabander were enantiomeric with the actual absolute configuration.

**Biological Activity of Peloruside A**

In Northcote's initial communication, it was disclosed that peloruside A was cytotoxic to p388 murine leukemia cells at a concentration of 10 ng/mL (18 nM).[3] Subsequent experiments revealed that peloruside A acts to stimulate microtubule polymerization, which causes cell cycle arrest during the $G_2$/M phase, triggering apoptosis.[6] When

(4) Stocker, B. L. *Ph.D. Thesis*, Victoria University of Wellington, **2004**. P 46

(5) Liao, X.; Wu, Y.; De Brabander, J. K. *Agnew. Chem. Int. Ed.* **2003**, *42*, 1648- 1652.

(6) Hood, K. A.; West, L. M.; Rouwé, B. Northcote, P. T.; Berridge, M. V.; Wakefield, St. J.; Miller, J. H. *Canc. Res.* **2002**, *62*, 3356-3360.

allowed to compete with the microtubule stabilizers paclitaxel (Taxol®) (**4**) epothilone A, (**5)** and (+) discodermolide (**6)**, shown in Figure 1.2, it was found that peloruside A bound at a different site.[7] This was deduced because of the presence of microtubules that incorporated stoichiometric amounts of both paclitaxel and peloruside A. Molecules **4**, **5** and **6** compete for the same binding site so only one of each molecule binds to any one microtubule.

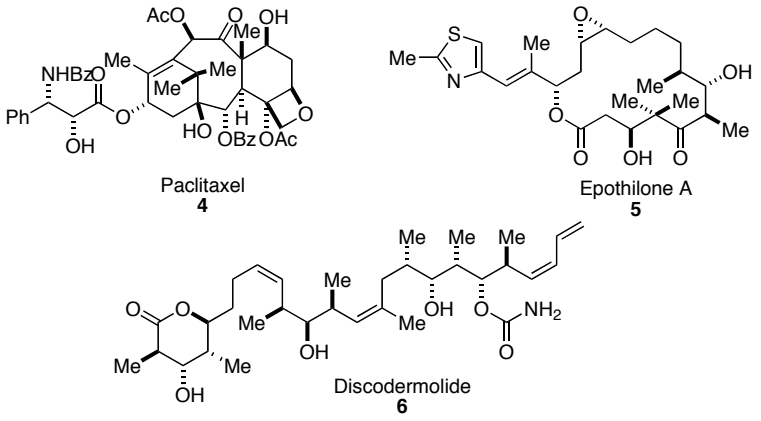



**Figure 1.2** Compounds with similar mode of action to peloruside A.

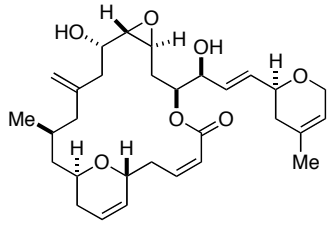
Most microtubule binding agents compete with the prototypical paclitaxel binding site on microtubule constituent β-tubulin, while initial NMR and molecular modeling studies suggest that peloruside A binds to α-tubulin.[8] Later experiments by Huzil and co-workers suggested that peloruside A binds to a non-taxoid site on β-tubulin on the basis of hydrogen-deuterium exchange mass spectrometry.[9] These experiments used a mass spectrometry/ protein sequencing approach to identify binding sites based on amino acid residues that are deficient in deuterium labeling after a deuterium exchange on the subject protein bound to the ligand. The ligand physically blocks deuterium exchange.

(7) Gaitanos, T. N.; Buey, R. M.; Díaz, J. F.; Northcote, P. T.; Teesdale-Spittle, P.; Andreu, J. M.; Miller, J. H. *Canc. Res.* **2004**, *64*, 5063-5067.

(8) Jiménez-Barbero, J.; Canales, A.; Northcote, P. T.; Buey, R. M.; Andreu, J. M.; Díaz, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8757-8765.

(9) Huzil, J. T.; Chik, J. K.; Slysz, G. W.; Freedman, H.; Tuszynski, J.; Taylor, R. E.; Sackett, D. L.; Schriemer, D. C. *J. Mol. Biol.* **2008**, *378*, 1016- 1030.

Subsequent work with both molecular modeling and experiments with synthetic tritiated [$^3$H] peloruside A appear to support the presence of the site on β-tubulin.[10] Cell lines that contain mutations in the site on β-tubulin that is believed to bind peloruside A were found to have resistance to the action of peloruside A.[11]An unusual mode of action such as this has implications for the discovery of new drugs that target cell lines that have become resistant to drugs such as paclitaxel. A different binding site on tubulin may not have developed the same mutations that confer resistance. This raises the potential that peloruside A or analogues could be used to treat paclitaxel resistant cancers. Another molecule, laulimalide (**7**), is also believed to bind to the same site as peloruside A (Figure 1.3). Laulimalide does compete with Peloruside A in microtubule binding experiments, however it is much less stable in solution and is not considered a good drug candidate.[6,10]




Laulimalide
**7**

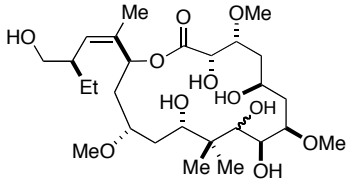
**Figure 1.3** Structure of laulimalide.

Studies on both synthetic and semisynthetic analogues of peloruside A have indicated that the tetrahydropyran moiety is crucial to the activity of peloruside A. Semisynthetic analogue **8**, prepared by $NaBH_4$ reduction of peloruside A was reported to have a 26 fold decrease in cytotoxicity,[6] while synthetic analogue **9** was found to be several hundred-fold less potent (Figure 1.4).[12]

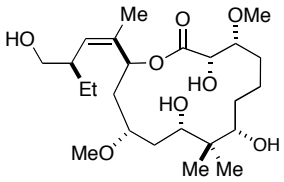
(10) Nguyen, T. L.; Xu, X.; Gussio, R.; Ghosh, A. K.; Hamel, E.; *J. Chem. Inf. Model.* **2010**, *50*, 2019-2028.

(11) Begaye, A.; Trostel, S.; Zhao, Z.; Taylor, R. E.; Schriemer, D. C.; Sackett, D. L. *Cell Cycle*. **2011**, *10*, 3387-3396.

(12) Wullschleger, C. W.; Gertsch, Altmann, K.-H. *Org Lett.*, **2010**, *12*, 1120-1123.



**8**

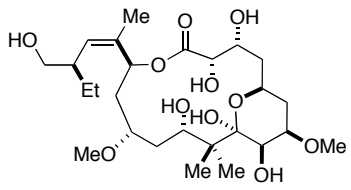


**9**

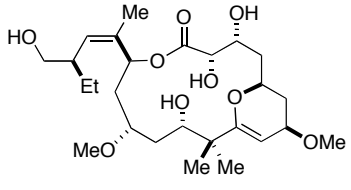
**Figure 1.4** Less potent analogues of peloruside A.

**Attempts to Produce Peloruside A via Aquaculture**

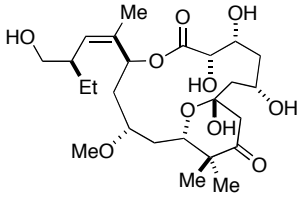
In light of the promising biological activity of peloruside A, efforts were made to cultivate the *M. hentscheli* species from which it was isolated.[13] These efforts were partially successful, allowing the cultivation of less than 7.5 kg of sponge, from which 85.5 mg of peloruside A could be isolated. The large-scale isolation also allowed the discovery of related compounds peloruside B, **10**, peloruside C, **11**, and peloruside D, **12**, shown in Figure 1.5.[14] These compounds were isolated in sub milligram amounts. Peloruside C was found to be active against a human myeloid leukemia cell line (HL-60) with an $IC_{50}$ value of 221 nM, which was 15 times less potent than the activity of peloruside A in the same assay. It was observed that HL-60 cells treated with **11** were not arrested at the $G_2$/M cycle, suggesting a different mode of action than peloruside A. Peloruside D was not significantly active against the HL-60 line. These results are in line with the notion that the tetrahydropyran moiety must be conserved for biological activity.



Peloruside B
**10**



Peloruside C
**11**



Peloruside D
**12**

**Figure 1.5** Structures of pelorusides B- D.

(13) Page, M. J.; Northcote, P. T.; Webb, V. L.; Mackey, S.; Handley, S. J.; *Aquaculture*, **2005**, *250*, 256-269.

(14) Singh, A.J.; Razzak, M.; Teesdale-Spittle, P.; Gaitanos, T. N.; Wilmes, A.; Paterson, I.; Goodman, J. M.; Miller, J. H.; Northcote, P. T. *Org. Biomol. Chem.* **2011**, *9*, 4456- 4466.

Aquaculture attempts were complicated by the observation that the production of peloruside A in cultured *M. hentscheli* was specific to both the geographical area in which the sponge was cultivated (removal of the sponge to a different bay resulted in cessation of peloruside A production) and the specific strain of *M. hentscheli* (moving a sponge originating from a geographically distant location into the Pelorus sound did not result in the commencement of peloruside A production). It is unclear if this is due to the presence of a symbiotic organism or environmental factors.[15] Until this problem is solved, it appears that total synthesis of peloruside A may be the most efficient way of obtaining multi-milligram quantities of this compound.

## II. Brief Summary of Approaches to Peloruside A

In light of the relatively simple structure of peloruside A, coupled with its promising biological activity, a number of synthesis efforts towards this target were initiated.

The purpose of this section is to summarize all disclosed completed total syntheses of peloruside A, and selected incomplete efforts with chemistry bearing similarities to our own route. It should not be considered a comprehensive summary. Complementary summaries may be found in selected Ph.D theses of other students who have worked on peloruside A.[16] It should be noted that $C_9$ of peloruside A is at the ketone oxidation state. Most of the synthesis work summarized below does not maintain this oxidation state throughout the synthesis. While the stereochemistry at this position in the alcohol oxidation state is ultimately inconsequential, it can have a very important effect on the stereoselectivity of reactions as described in great detail in section IV of this chapter. Accordingly this is emphasized where appropriate.

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(15) Page, M. J.; West, L.; Northcote, P. T.; Battershill, C.; Kelly, M. *J. Chem. Ecol.* **2005**, *31*, 1161-1174.

(16) Wuest, W. M. *Ph.D. Thesis*, University of Pennsylvania, **2008**. Engers, D. W. *Ph.D. Thesis*, University of Texas at Austin, **2006**. Jeon, J. *Ph.D. Thesis*, University of Minnesota, **2009**. Xu, X. *Ph.D. Thesis*, Purdue University, **2008**. McGowan, M. A. *Ph.D. Thesis,* Harvard University, **2010**. Schiffler, M. A., *Ph.D. Thesis,* Harvard University, **2008**.

## The DeBrabander Synthesis

The first synthesis of peloruside A to be disclosed was that of DeBrabander in 2003.[5] The synthesis established the absolute configuration of peloruside A, as the synthesis resulted in material with the opposite optical rotation as the natural material. The intermediates in the configuration used by DeBrabander en route to *ent*-peloruside A are shown below (Figure 1.6). De Brabander's approach involved a late stage macrocyclization of a seco acid **13** with a fully elaborated pyran component. Coupling fragments **14** and **15** in an aldol reaction assembled this seco acid.

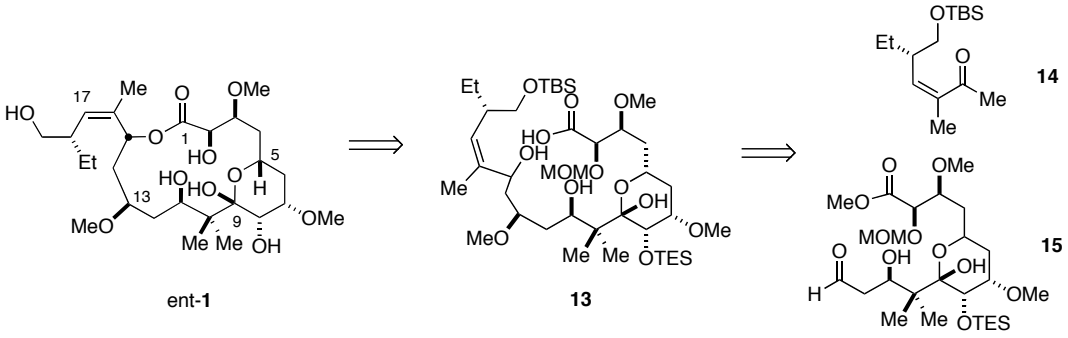
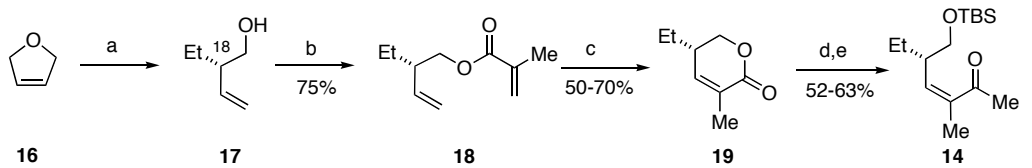


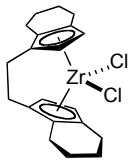

**Figure 1.6** De Brabander's synthesis plan.

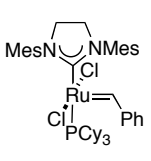
The synthesis of fragment **14** was comparatively short and is shown in Scheme 1.1. The stereocentre at $C_{18}$ was set by a Hoveyda ethylmagnesiation on 2,5-dihydrofuran **16** generating alcohol **17** in 99% ee. Acylation with methacroloyl chloride yielded diene **18**. This was followed by a ring closing metathesis using Grubbs' second generation catalyst to yield lactone **20**, followed by conversion of the lactone to a methyl ketone and protection of the resultant alcohol yielding fragment **14** in only 5 steps.

**Scheme 1.1**




a) 5 mol% **20**, EtMgCl, THF; b) $CH_2CMeC(O)Cl$, DMAP, *i*$Pr_2NEt$, $CH_2Cl_2$, c) 10 mol% **21**, 0.0025 $MCH_2Cl_2$, d) MeLi, -78 °C, pentane e)TBSCl, im, DMAP, DMF



The synthesis of fragment **15** was more involved. The important disconnections are shown in figure 1.7. Stereochemistry was controlled by the use of asymmetric allylation reactions/ oxidative olefin cleavage as aldol surrogates, and a substrate controlled epoxidation and allylation. A notable point was the successful use of a MOM group to protect the hydroxyl at $C_2$.

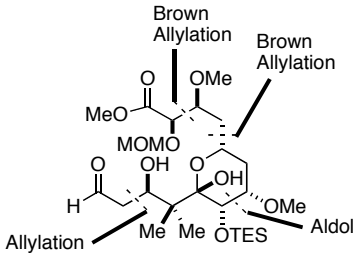
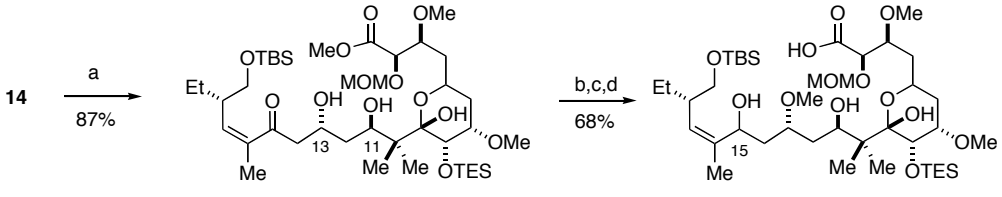



**Figure 1.7** Bond constructions in fragment **15**.

The bond construction between $C_{13}$ and $C_{14}$ involved an aldol reaction mediated by $Et_2BOTf$ in the presence of a free alcohol at $C_{11}$ on fragment **15**. The aldol reaction proceeded in good yield (87%) with modest diastereoselectivity to afford aldol adduct **22**. A selective methylation of the $C_{13}$ alcohol was followed by reduction of the $C_{15}$ ketone with CBS catalyst and hydrolysis of the $C_1$ methyl ester gave seco acids **23** and **24** (Scheme 1.2). Both configurations of the alcohol at $C_{15}$ could be accessed depending on which antipode of the CBS catalyst was used.

**Scheme 1.2**

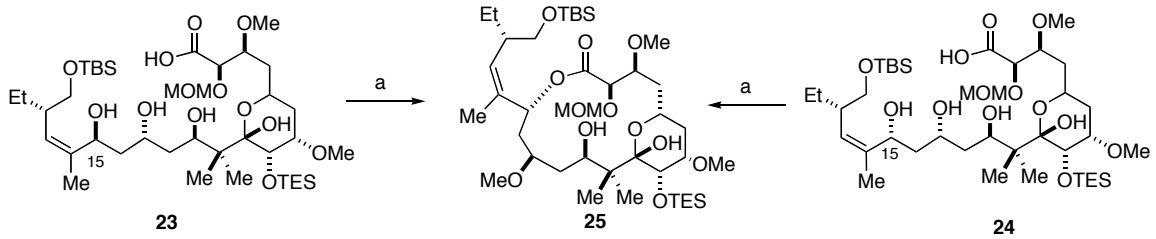



a) *i*$Pr_2NEt$, $Et_2BOTf$, $CH_2Cl_2$, then add **15**, 2:1 dr b) 20 eq $Me_3OBF_4$, 2,6-di-*tert*-butyl-4-methylpyridine, $CH_2Cl_2$, c) (*R*) or (*S*) B-Me CBS catalyst (see text), $BH_3SMe_2$ $CH_2Cl_2$ d)0.3 N $LiOH_{(aq)}$, THF

Seco acids **23** and **24** could be subject to a Mitsunobu macrolactonization. Interestingly both seco acids converged to give a common product, macrolactone **25**, which means that seco acid **23** is undergoing an invertive Mitsunobu reaction, while seco acid **24** is undergoing a Mitsunobu reaction with retention. The yields were 47% for each seco acid,

rising to 52% on a 1:1 mixture of the two (Scheme 1.3). DeBrabander speculates that the retentive Mitsunobu proceeds through an acyloxophosphonium intermediate. An alternative explanation is that **24** is not stereoelectonically disposed to undergo a $S_{N2}$ reaction, so the intermediate ionizes and an attack of the carboxylate on the allyl cation proceeds with retention of stereochemistry.

**Scheme 1.3**




**23** **25** **24**

a) $PPh_3$, DIAD, THF (0.05 M), add seco acid (0.003 M in THF) over 2h at 0 °C

The final macrolactone **25** was deprotected by exposure to 4N HCl in THF, which established the robustness of peloruside A to these conditions. DeBrabander's synthesis showed the viability of using 4N HCl in the deprotection, the possibility of using a MOM group to protect the hydroxyl at $C_2$ and also proved both the stereochemical assignment and the absolute configuration of peloruside A. The synthesis had a longest linear sequence of 32 steps, with an impressive overall yield of 1.5% based on multiplication of the yields given in the paper.

**The Taylor Synthesis**

In 2005, the Taylor group disclosed their synthesis of peloruside A.[17] This synthesis involved a late stage elaboration of pyranone macrocycle **26** shown in Figure 1.8. The synthesis of **26** relied on the macrocyclization of a pyranone containing seco acid **27**. The seco acid was assembled from two fragments, $C_8$–$C_{19}$ fragment **28** and $C_1$–$C_7$ fragment **29** by a lithium aldol reaction. The $C_8$–$C_{19}$ fragment was assembled using similar

(17) Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303-1305.

chemistry to our $C_{10}$–$C_{19}$ fragment (*vide infra*)[18] while the $C_1$ to $C_7$ fragment arose an epoxide opening and Evans aldol sequence.

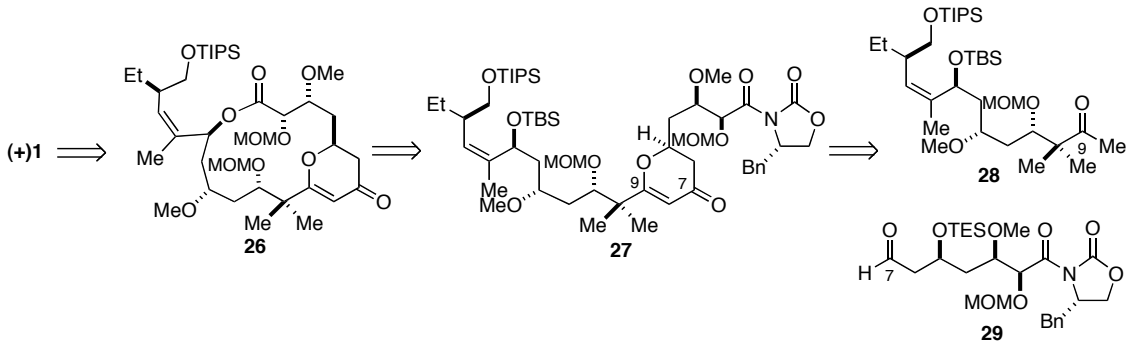
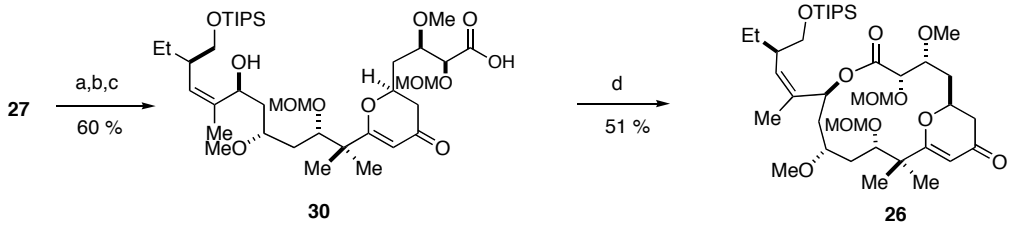



**Figure 1.8** Taylor retrosynthesis.

The key fragment coupling between fragment **28** and **29** was accomplished by a lithium aldol reaction, followed by oxidation of the aldol product to a 1,3 diketone, followed by deprotection of the TES protected alcohol at $C_5$ and cyclization to form a pyranone (Scheme 1.4). Deprotection of the TBS group protecting the alcohol at $C_{15}$, followed by cleavage of the oxazolidinone at $C_1$ yielded seco acid **30**. This was subject to a Yamaguchi reaction to produce macrolactone **26**.

**Scheme 1.4**

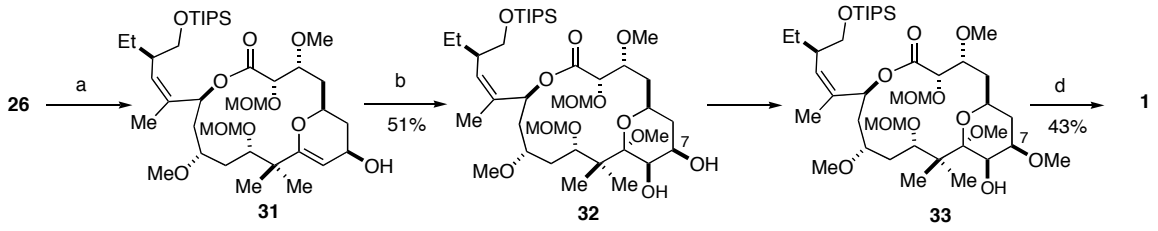



a) HF•py b) TIPSCl, *i*$Pr_2$NEt, $CH_2Cl_2$ c) LiOH, THF/DMF d) 2,4,6-trichlorobenzoyl chloride, DMAP

Macrolactone **26** was then elaborated by a Luche reduction to compound **31** (Scheme 1.5). Directed epoxidation and methanolysis yielded diol **32**. Selective methylation of the equatorial alcohol at $C_7$ afforded macrolactone **33**. Deprotection with 4N HCl gave peloruside A.

(18) Taylor, M. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959- 4961.

**Scheme 1.5**




a) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, MeOH b) MCPBA, then MeOH, c)$Me_3OBF_4$, Proton Sponge ®, d) 4N HCl

The Taylor synthesis is most noteworthy in that the synthesis of fragment **28** bears co-incidental similarities to the synthesis of our $C_{19}$–$C_{10}$ fragment. This synthesis also showed that an oxazolidinone at the $C_1$ terminus could be carried through several steps. The Taylor synthesis had a longest linear sequence of 30 steps, with an overall yield of 0.38% based on multiplication of reported yields of the longest linear sequence.

**The Ghosh Synthesis**

The Ghosh Synthesis was disclosed in 2007, while our second generation effort was underway.[19] The synthesis of late stage macrocycle **34** is notable as it is the first disclosed synthesis to rely on a macrolactonization of a seco acid **35** that does not contain a pyran, with formation of the pyran after macrolactonization (Figure 1.9).[20] This is also the strategy we employed. However, the Ghosh seco acid does contain acetonide protection of the $C_7$ and $C_8$ alcohols, which introduces a cyclic templating element. The linear seco acid is generated from a reductive aldol coupling of $C_1$–$C_{10}$ fragment **36** and $C_{11}$–$C_{19}$ fragment **37**. Fragment **36** was prepared in 21 steps from tartaric acid while fragment **37** was prepared in 12 steps by an iterative allylation strategy.[21]

(19) Ghosh, A. K.; Xu, X.; Kim, J.-H.; Xu, C.-X. *Org. Lett.* **2008**, *10*, 1001-1004.

(20) It should be noted our group's first generation strategy employing the cyclization of a linear seco acid, followed by pyran formation during the global deprotection had resulted in a successful synthesis of Peloruside A by Dr. Dennie Welch prior to Ghosh's disclosure.

(21) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 7659-7662.

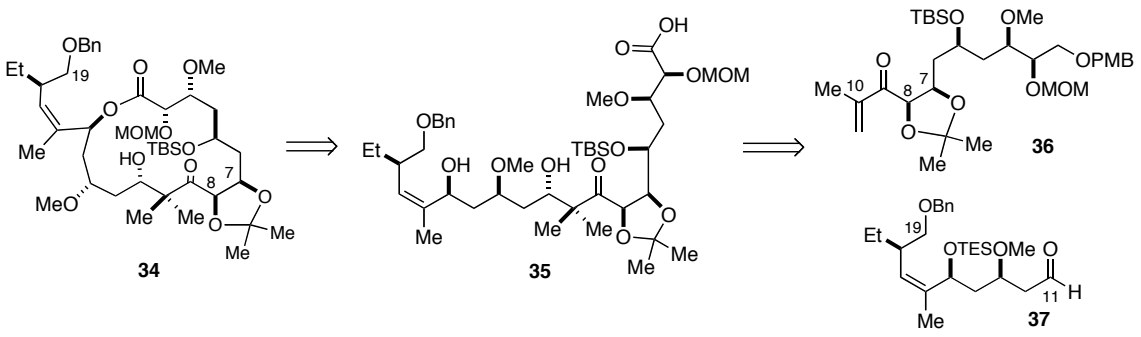
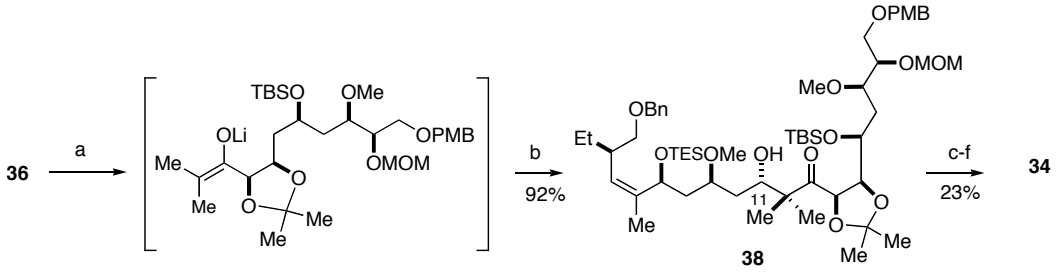



**Figure 1.9** Ghosh synthesis plan.

In the forward direction, synthesis proceeded by treatment of fragment **36** by L-selectride, which resulted in the formation of an enolate from 1,4 addition of the hydride (Scheme 1.6). Addition of fragment **37** resulted in aldol adduct **38** in 92% yield with a 5:1 dr. Throughput for the synthesis was affected by a low yield for conversion of the aldol product to macrolactone **34** (23% over 3 steps). The necessity of having $C_1$ in the alcohol oxidation state was presumably dictated by the reducing conditions of the fragment coupling. Selective macrolactonization for the $C_{15}$ alcohol occurred despite the presence of a free alcohol at $C_{11}$.

**Scheme 1.6**

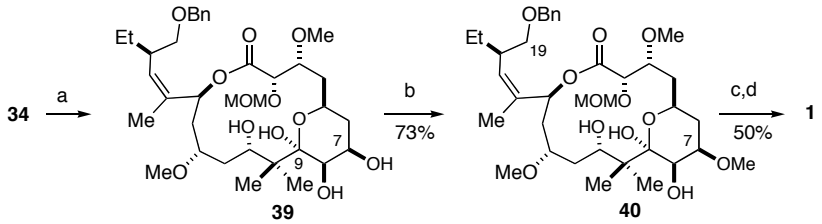



a) L-selectride, $Et_2O$, -78 °C b) add **37**(1:5 dr) c) DDQ , aq. THF, then DDQ, $CH_2Cl_2$ d)TPAP, NMO e)$NaClO_2$, $NaH_2PO_4$ f) 2,4,6-trichlorobenzoyl chloride, DMAP, tol.

After the macrocyclization, several steps were needed to complete the synthesis (Scheme 1.7). Concomitant deprotection of the acetonide protecting the alcohols at $C_7$ and $C_8$ and the TBS group protecting the alcohol at $C_5$ resulted in the cyclization of the $C_5$ alcohol on to the $C_9$ ketone to form pyran **39**. Selective methylation of the equatorial alcohol at $C_7$ yielded protected peloruside A **40**, which was deprotected by transfer hydrogenolysis of

the $C_{19}$ benzyloxy protecting group followed by cleavage of the MOM group protecting the alcohol at $C_2$ with 4N HCl to yield peloruside A.

**Scheme 1.7**




a) 1N HCl, THF b)$Me_3OBF_4$, 2,6-di*tert*butylpyridine, c)Pd/C, MeOH, HCOOH, d) 4N HCl, THF

The Ghosh Synthesis was the first synthesis disclosed that employed macrocyclization of a seco acid in the absence of the pyran moiety. The reductive aldol fragment coupling and protection of the $C_{19}$ alcohol as a benzyloxy group were also used in the Jacobsen synthesis (*vide infra*). Several oxidation state manipulations and short homologations affect material throughput of this synthesis. The longest linear sequence was 30 steps with an overall yield of 1.1%, obtained by multiplying the reported yields along the longest linear sequence.

**The Evans Synthesis**

The Evans first generation synthesis of peloruside A, completed by Dr. Dennie Welch followed the Taylor synthesis and preceded disclosure of the Ghosh synthesis. This work is described in Section IV of this chapter. The second-generation synthesis strategy, developed by Dr. Dennie Welch and implemented by Dr. Dennie Welch, Stephen Ho and myself was published in February 2009 and is described in Chapter 2.[1]

**The Jacobsen Synthesis**

The synthesis of peloruside A by the Jacobsen group was disclosed in May of 2010.[22] Their strategy involved cyclization of a linear seco acid, which was constructed through a reductive aldol coupling of $C_1$–$C_{10}$ fragment **42** with $C_{11}$–$C_{19}$ fragment **43** (Figure 1.10).

(22) McGowan, M. A.; Stevenson, C. P.; Schiffler, M. A.; Jacobsen, E. N.; *Angew. Chem. Int. Ed.* **2010**, *49*, 6147- 6150.

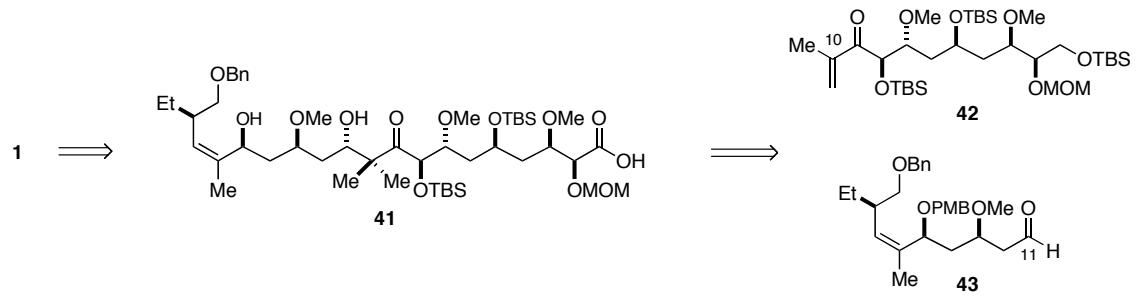
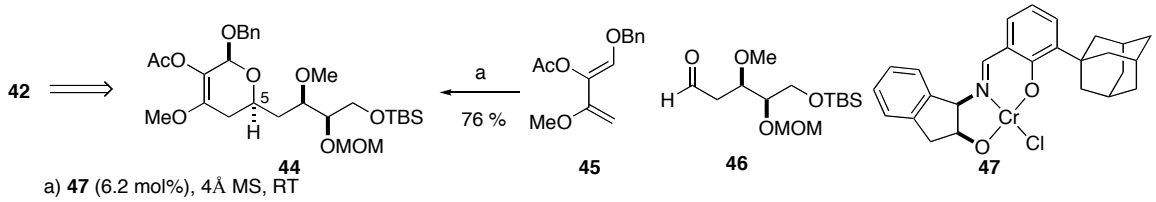


**Figure 1.10** Jacobsen retrosynthesis.

The synthesis of fragments **42** and **43** showcased a number of transformations mediated by salen catalysts. The synthesis of fragment **42** was from hetero Diels–Alder adduct **44** arising from diene **45** and aldehyde **46** (Scheme 1.8). Catalyst control by **47** enabled a 7:1 dr in the Diels–Alder reaction, while the natural bias of **46** as explored by an achiral catalyst was 1:2 dr the other way.

**Scheme 1.8**



Fragment **43** was obtained in 9 steps from epoxide **48**, obtained via a 2 step Jacobsen epoxidation/ HKR sequence on pent-1-en-3-yne **49**. Another epoxide, obtained in high optical purity by HKR on the racemate was also employed in the synthesis of this piece.

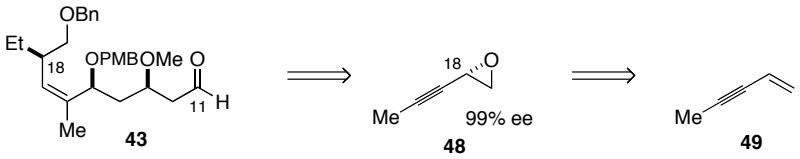
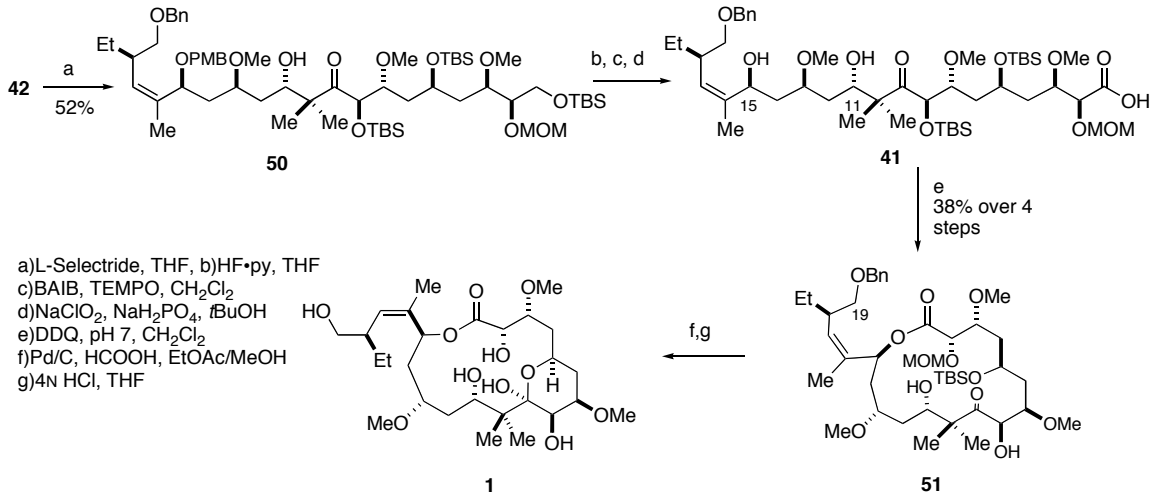


**Figure 1.11** Retrosynthesis of fragment **43**.

Fragment coupling was conducted using a reductive aldol reaction employing L-Selectride similar to the Ghosh reaction. Unfortunately only a modest diastereoselectivity of 1.7 to 1 was obtained, with the overall yield of the desired product **50** being 52%. Subsequently the TBS protected $C_1$ alcohol was selectively deprotected and oxidized in a 2-step sequence, which after deprotection of the PMB group afforded seco acid **41**

(Scheme 1.9). Macrocyclization using Yamaguchi conditions led to protected peloruside A **51**. As with our synthesis, the macrolactonization was site selective for the alcohol at $C_{15}$ despite the presence of free alcohol at $C_{11}$. Compound **51** was deprotected in a 2-step hydrogenolysis/ 4N HCl sequence in a manner reminiscent of Ghosh to afford peloruside A.

**Scheme 1.9**




The Jacobsen route is noteworthy for being the shortest disclosed route at 20 longest linear steps. Unfortunately the modest diastereoselectivity in the reductive aldol based $C_{10}$–$C_{11}$ bond construction and the necessity to adjust the $C_1$ oxidation state late in the synthesis because of the use of the reductive aldol coupling detract from the efficiency of the synthesis. Regardless, the synthesis had an impressive longest linear sequence of 20 steps, with an overall yield of 0.7% based on multiplication of the yields reported for steps on the longest linear sequence. The yield rises to 1.2% if the yield of the first step (the enantioselective Payne reaction, followed by protection, overall yield 56% is omitted).[23]

(23) It is preferable to have a low yielding step at the beginning or end of a synthesis, since if the step is at the beginning there should be a low material cost, allowing large scale reactions to provide ample material. For synthesis where the goal is to attain the target, and not generate large quantities of material for further study, if the problematic step is at the end, a bottleneck is not created as material throughput for subsequent steps is not required.

**The Hoye Synthesis**

The Hoye synthesis was disclosed in July 2010 after the Jacobsen synthesis.[24] Their synthesis strategy also involved macrocyclization of a linear seco acid **52** (Figure 1.12). This was prepared from a fragment coupling between a $C_1$–$C_{11}$ fragment **53** and a $C_{12}$–$C_{19}$ fragment **54**. This disconnection is also the one employed in our synthesis, and in fact their fragment **54** is identical to ours, although prepared by a different route. Special attention will be given to this bond construction since it was successful with $C_9$ in the alcohol oxidation state, while this transformation failed in a very similar substrate in our case (this will be discussed in section II of chapter 2).

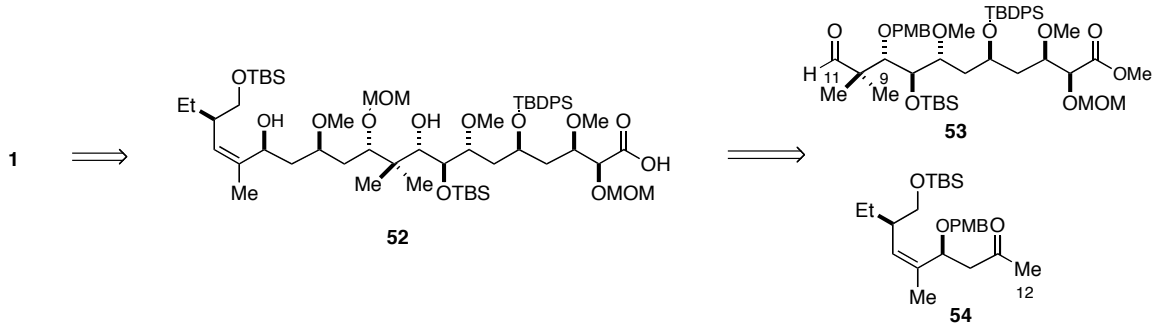



**Figure 1.12** Hoye retrosynthesis.

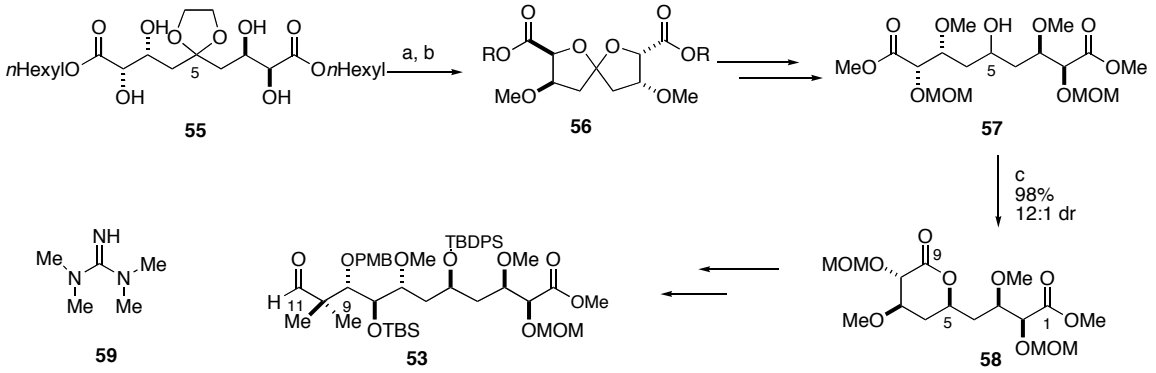
The synthesis of the aldehyde in **53** was from an ozonolysis of an alkene and the methyl ketone in **54** arose from Wacker oxidation of an alkene. This meant that doing an ozonolysis on the precursor to **54** and Wacker on the precursor to **53** would have allowed exploration of a $C_{12}$–$C_{13}$ bond disconnection.

The synthesis of fragment **53** began with $C_2$ symmetric tetraol **55**, prepared by a Sharpless asymmetric dihydroxylation of the corresponding di-enoate (Scheme 1.10). Differentiation of the diols was achieved by transketalization followed by methylation to afford **56**. Subsequently, **56** was elaborated to alcohol **57** in 5 steps. Pseudo-symmetric

(24) Hoye, T. R.; Jeon, J., Kopel, L. C.; Ryba, T. D.; Tennakoon, M. A.; Wang, Y. *Angew. Chem. Int Ed.* **2010**, *49*, 6151-6155.

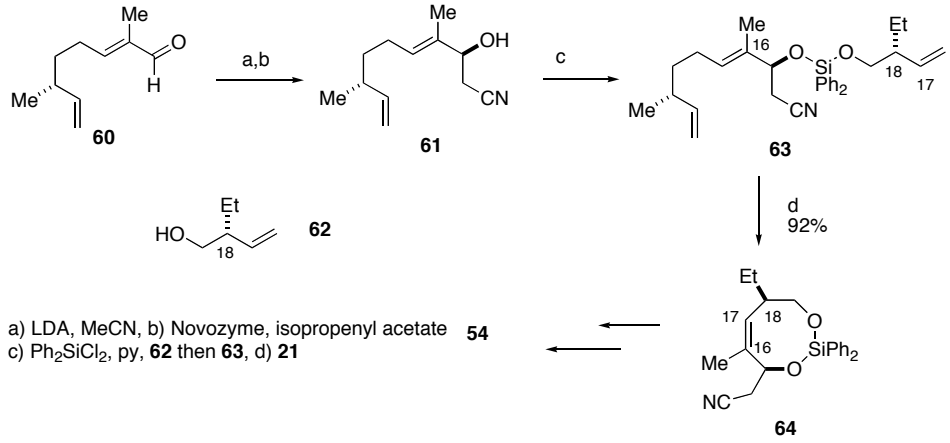
alcohol **57** was transformed to compound **58** by a diastereoselective lactonization, which sets the stereochemistry at $C_5$ as the compound no longer possesses an axis of symmetry through this carbon. The translactonization was mediated by tetramethylguanidine **59**. A 15 step sequence then allowed this intermediate to be converted to fragment **53**.

**Scheme 1.10**



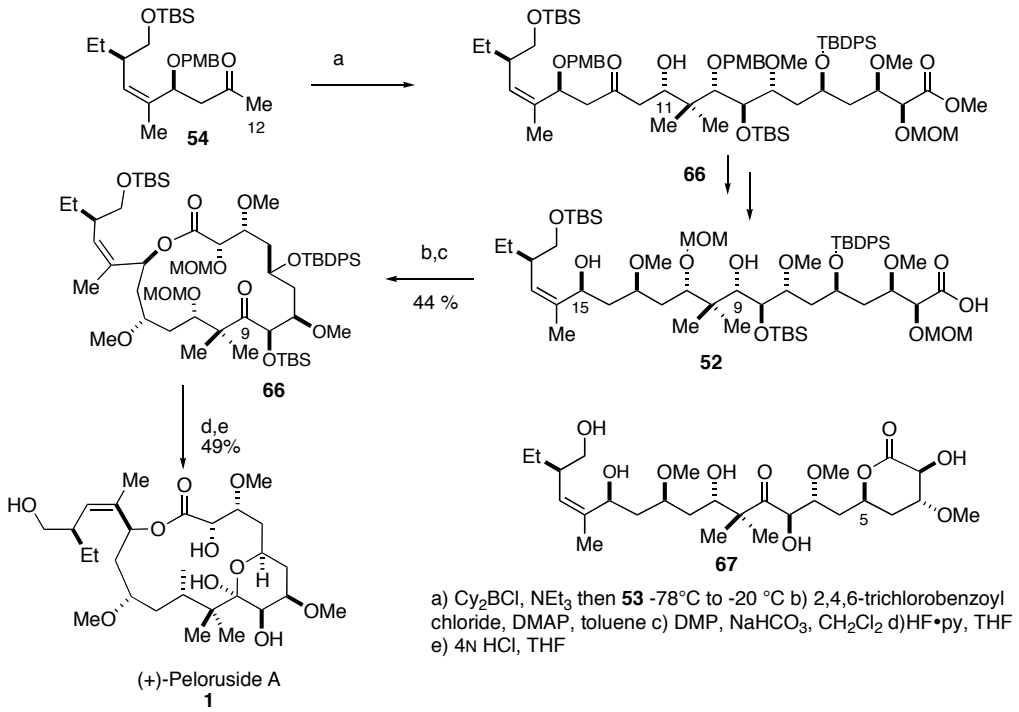

The synthesis of fragment **54** involved the addition of the anion of acetonitrile to an aldehyde **60** derived from (*R*)- citronellene (Scheme 1.11). The epimeric alcohols at $C_{15}$ were resolved by enzymatic means (Novozyme 453). Subsequent tethering of this diastereomerically pure alcohol **61** with alcohol **62** via a silicon tether yielded diene **63**, which was subject to relay ring closing metathesis to yield 8 membered ring **64** that was converted to fragment **54** in 5 steps. The structure and spectra of this fragment matched our corresponding fragment (See Scheme 1.20).

**Scheme 1.11**



The fragment coupling was mediated by $Cy_2BCl$ and $Et_3N$ in diethyl ether giving **65** in essentially perfect diastereoselection at $C_{11}$ in 62% yield (Scheme 1.12). It is very interesting that this fragment coupling was successful. As will be explained more fully in section III of chapter 2, a fragment coupling attempt in our route under the same conditions with the same fragment **54**, and a version fragment **53** differing only in the substituents at $C_9$, $C_5$ and $C_1$ showed no reactivity at all. After the fragment coupling, a 5-step sequence afforded seco acid **52**. This was cyclized under Yamaguchi conditions with selective cyclization onto the $C_{15}$ alcohol despite the presence of a free alcohol at $C_9$. Oxidation of the $C_9$ alcohol afforded macrolactone **66**. The above sequence was followed by a 2 step global deprotection to afford peloruside A. Additionally, an isomer of peloruside A, **67** bearing a lactone cyclized onto the $C_5$ alcohol rather than the $C_{15}$ alcohol was obtained in low yield. It is likely that this material formed in other synthesis efforts as well, but was overlooked.

**Scheme 1.12**



The Hoye synthesis involved a clever desymmetrization of a pseudo $C_2$ symmetric $C_1$–$C_9$ compound. Unfortunately material throughput was affected by the lengthy sequence required to convert this compound to fragment **53**. The fragment coupling between **53** and **54** was remarkable as it revealed very subtle protecting group effects when coupled with data from our group. The Hoye synthesis had a longest linear sequence of 36 steps, with an overall yield calculated from multiplication of reported yields on the longest linear sequence of 0.36%.

**The Smith Approach**

The Smith group approach involved a cyclization of a linear seco acid **68** prepared from $C_1$–$C_8$ fragment **69** and $C_9$–$C_{19}$ fragment **70** (Figure 1.13).[25] This fragment coupling was conducted by the addition of the anion of a dithiane into an aldehyde. Fragments **69** and **70** were also prepared using anion relay chemistry involving the alkylation of silylated dithiane anions by epoxides followed by Brook rearrangement.

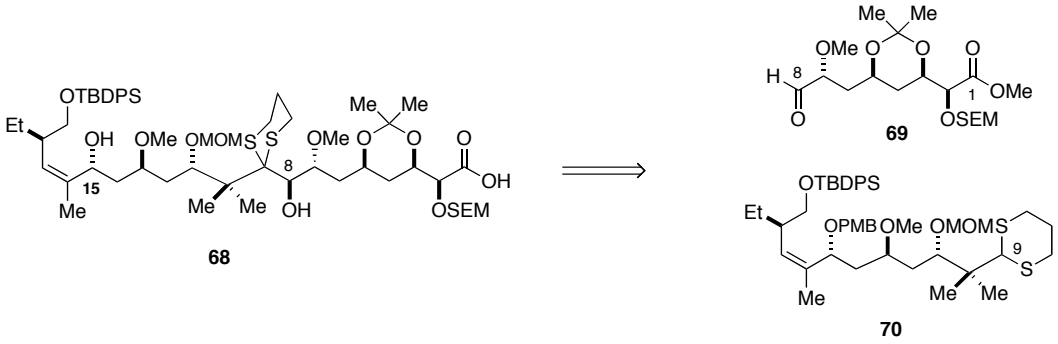


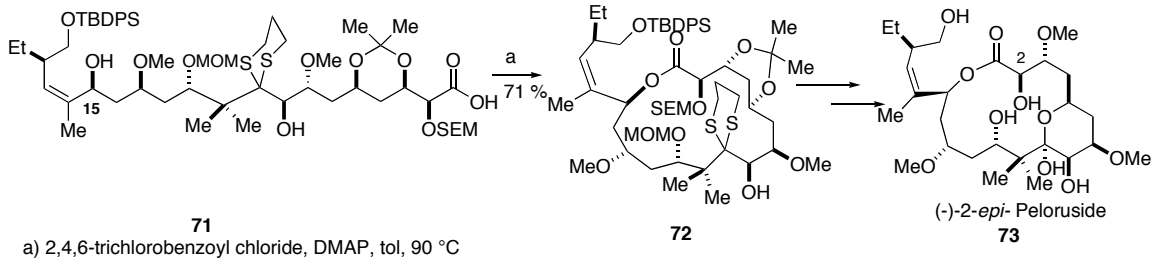

**Figure 1.13** Smith synthesis plan.

The cyclization of the seco acid **68** initially involved the use of a Mitsunobu macrocyclization (Scheme 1.13). Contrary to DeBrabander's substrates, a substrate designed for cyclization via inversion at $C_{15}$ failed to macrolactonize. The epimer at $C_{15}$, **71**, was prepared by an oxidation/CBS reduction sequence, and could cyclized using a Yamaguchi reaction to give macrocycle **72**, however forcing conditions were required. A

(25) Smith, A. B.; Cox, J. M.; Furuichi, N.; Kenesky, C. S.; Zheng, J.; Atasoylu, O.; Wuest, W. M. *Org. Lett.* **2008**, *10*, 5501- 5504.

3-step sequence resulted in the synthesis of compound **73** that was epimeric with peloruside A at $C_2$.

Scheme **1.13**




**71**

a) 2,4,6-trichlorobenzoyl chloride, DMAP, tol, 90 °C

**72**

(-)-2-*epi*- Peloruside

**73**

Extensive NMR and computational studies suggested that the epimerization had taken place during the forcing conditions of the Yamaguchi macrolactonization.

**The Paterson Approach**

An approach to peloruside A by the Patterson group was disclosed in 2003.[26] The Patterson synthesis analysis targeted a linear seco acid **74**, constructed through the same bond disconnections as our second generation strategy, namely an aldol construction between $C_6$ and $C_7$ followed by elaboration and then an aldol disconnection between $C_{11}$ and $C_{12}$ (Figure 1.14). This strategy was devised before the absolute configuration of Peloruside A was known, so the structures shown are in the configurations as prepared by Paterson.

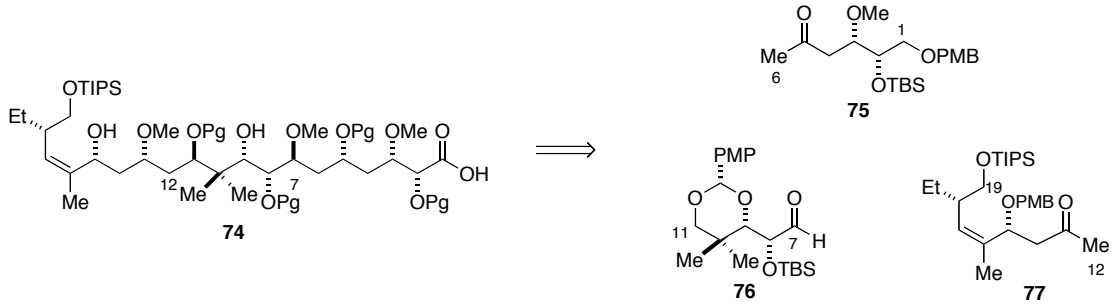



**Figure 1.13** The Paterson synthesis plan.

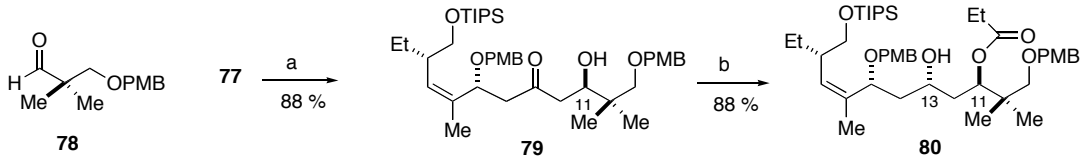
The $C_1$–$C_6$ fragment **75** was prepared in 12 steps from methyl acetoaceonate employing a Sharpless asymmetric dihydroxylation to set the stereocentres at $C_2$ and $C_3$.

(26) Paterson, I.; Di Francesco, E. M.; Kühn, T. *Org. Lett.* **2003**, *5*, 599- 602.

The $C_7$–$C_{11}$ fragment **76** was prepared in 8 steps from neopentyl glycol, also using a Sharpless asymmetric dihydroxylation to set the stereocentres at $C_8$ and $C_9$. This results in syn oxygenation, which has implications for the subsequent fragment coupling. Accessing the anti diol with this strategy would be difficult since *Z* dienes are poor substrates for the Sharpless asymmetric dihydroxylation.[27]

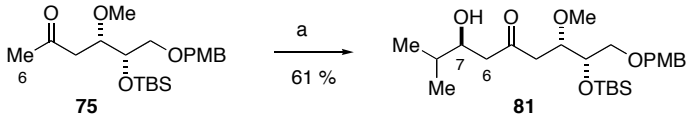
The $C_{12}$–$C_{19}$ fragment **77** was prepared in 10 steps employing a Paterson aldol. Paterson did not disclose full fragment couplings, but instead employed simple models for each fragment coupling. The fragment coupling of $C_{11}$–$C_{19}$ fragment **77** with model aldehyde **78**, derived from neopentyl glycol, was uneventful, proceeding in > 95:5 dr at $C_{11}$with 1,5 anti induction observed in aldol adduct **79** (Scheme 1.14). An Evans–Tishchenko reduction effectively relayed stereochemistry from the $C_{11}$ alcohol to the reduction of the $C_{13}$ ketone, enabling the construction of the $C_9$- $C_{19}$ fragment of peloruside A. This bears coincidental similarity to work conducted by Dr. George Moniz in this group that will be described in section III of this chapter.

**Scheme 1.14**




a) $Cy_2BCl$, $Et_3N$, $Et_2O$, -78 °C, then **78** b) $SmI_2$, EtCHO, THF

An aldol reaction with isobutyraldehyde and $C_1$-$C_6$ fragment **75** proceeded in modest yield 61% with a moderate (75: 25: preference for the desired diastereomer (equation 1.2).

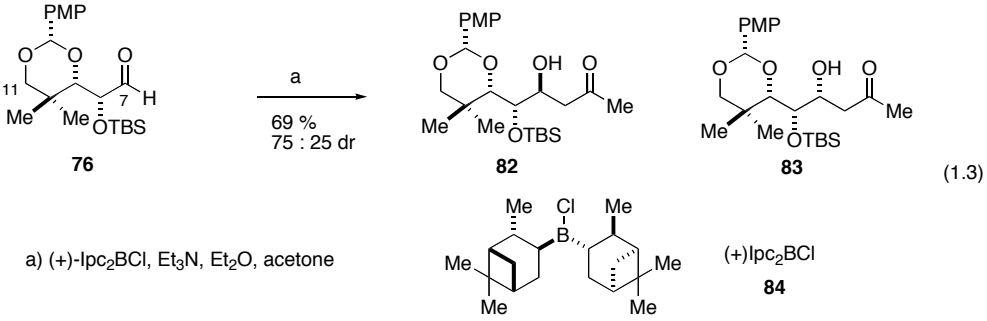



(1.2)

a) $Cy_2BCl$, $Et_3N$, $Et_2O$, -78 °C, *i*-PrCHO

(27) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T.; *J. Org. Chem*. **1991**, *56*, 4585- 4588.

The part with most significance to our route involved the attempts at the $C_6$–$C_7$ bond construction (equation 1.3). The addition of acetone enolates into the $C_7$ aldehyde **76** showed either no selectivity for the desired diastereomer **82** as with the $Cy_2B$ enolate (57: 43 dr for **82**: **83**), or the a preference for the incorrect diastereomer **83** as was seen with the lithium enolate (25: 75) or Mukaiyama conditions (7: 93). The only conditions that provided good selectivity for the desired diastereomer (75:25, 69% yield) required the use of (+)–$Ipc_2BCl$ **84** to produce a chiral enolate. Using (-)–$Ipc_2BCl$ overturns the selectivity (10:90, 88% yield).

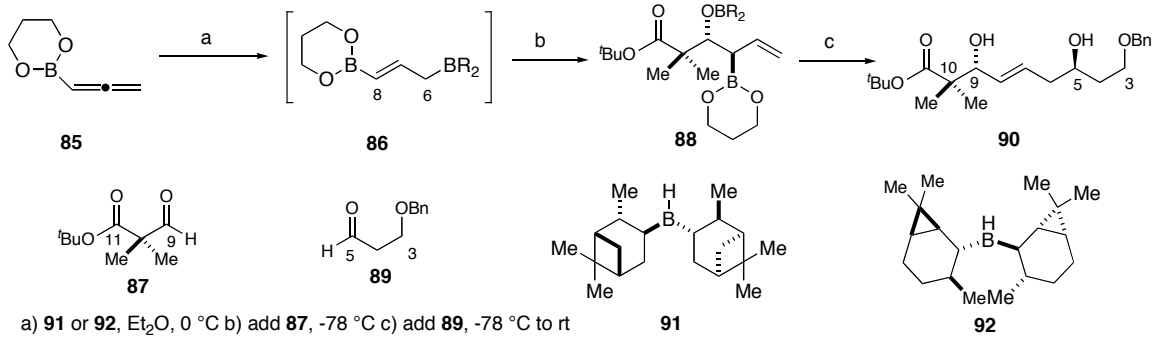



Paterson states that it may be anticipated that the use of chiral $C_1$–$C_6$ fragment **75** may enhance the diastereoselectivity of this step in a triple diasterodifferentiating aldol since **75** has a modest intrinsic preference for the desired outcome. The results in section III of this chapter will reveal that an anti disposition of the oxygenation at $C_8$ and $C_9$ is essential to obtaining high diastereoselectivity in the $C_6$–$C_7$ bond construction, so it is likely that this bond construction was not successful as planned. The Paterson approach is noteworthy in that it uses the same bond disconnections as our second-generation synthesis. Our findings that are reported in section I of chapter 2 suggest that Paterson would have encountered difficulties with a selective $C_6$–$C_7$ bond construction based on his choice of the configuration of the alcohol at $C_9$. It is also unclear from either our work or Hoye's work if the $C_{11}$ to $C_{12}$ bond construction will work with syn oxygenation at $C_8$ and $C_9$. Had the $C_9$ stereocentre been epimeric, Hoye's precedent suggests the fragment coupling would be successful, albeit with careful choice of protecting groups.

**The Roush Approach**

The Roush approach is notable in that it provides the most efficient reported synthesis of a $C_1$–$C_{11}$ fragment (Scheme 1.15).[28] This employs Roush's double allylboration methodology. Hydroboration of allenylborane **85** with a chiral borane delivers diboron intermediate **86** which is allowed to react with aldehyde **87**, derived from neopentyl glycol. This produces intermediate allylborane **88**, which is then allowed to react with aldehyde **89**. This produces a $C_3$–$C_{11}$ fragment **90** in one pot, with the correct stereochemistry at $C_5$ and diastereomer at $C_9$. Use of $(Ipc)_2BH$ **91** gave **90** in 77% yield with 85% ee, while use of $(2\text{-}^dIcr)_2BH$ **92** gave **90** in 36% yield in >95% ee. The decision was made to use the higher yielding reaction and separate diastereomers that would result from coupling with an enantiomerically pure piece at a later stage.

**Scheme 1.15**



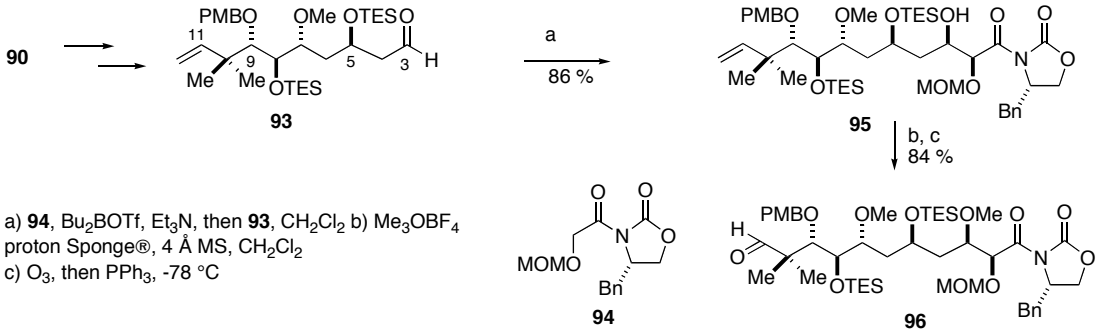

This fragment was elaborated in 11 steps to another $C_3$–$C_{11}$ fragment **93** bearing full oxygenation with appropriate protecting groups for further elaboration (Scheme 1.16).

This elaborated fragment was then subject to an glycolate Evans Aldol reaction with oxazolidinone **94** which provided aldol adduct **95** in an impressive 86% yield.[29] The minor diastereomer resulting from the fact the aldehyde was 85% ee was removed at this point. Subsequently the aldol adduct **95** was methylated and elaborated to aldehyde **96**.

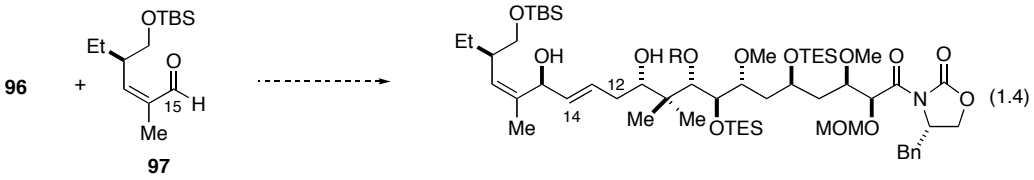
(28) Owen, R. M.; Roush, W. R.; *Org. Lett.* **2005**, *7*, 3941-3944.

(29) Typical yields for the glycolate aldol employed in our $C_2$ to $C_3$ bond construction on much simpler substrates were in the 60% range.

**Scheme 1.16**




The synthesis plan then involved conducting another double allylboration to combine $C_1$–$C_{11}$ aldehyde **96** and $C_{15}$–$C_{19}$ aldehyde **97**. The allylboration reagent would be the $C_{12}$–$C_{14}$ linker.




Given the difficulties we had with the $C_{11}$–$C_{12}$ bond construction with $C_9$ in the alcohol oxidation state, it can be anticipated that the Roush group would have run into difficulties with this transformation. The double allylboration provided an impressive route to a sparsely functionalized $C_3$-$C_{11}$ piece, and despite the 11 steps required to fully oxygenate this piece, the approach to this piece remains competitive to ours in both yield and step count.

## III. Summary of Evans Group's First Approaches[30]

### The Moniz Approach

Dr. George Moniz, a post-doctoral fellow in our group, initiated the peloruside project in 2001.[31] At the time the absolute configuration of peloruside A was not known, but Dr.

(30) A detailed summary of the approaches was prepared in the post-doctoral reports of Dr. George Moniz, Dr. Andreas Reichelt and Dr. Dennie Welch. Since this information is not available in the public domain, information most pertinent to the second generation synthesis designed by Dr. Dennie Welch is presented here. Accordingly this summary follows the same framework as that prepared by Dr. Dennie Welch although the prose and schemes are my own.

(31) Moniz, G. A. Postdoctoral Report, Harvard University, **2003**.

Moniz applied Celmer's rule to successfully predict the correct configuration.[32] Celmer's rule is based on the observation that a number of "unusual" macrolides, which have oxygenation at the $C_7$ position, usually in the L configuration, uniformly have an D-configuration at the macrolactone terminus in their Fischer projections.

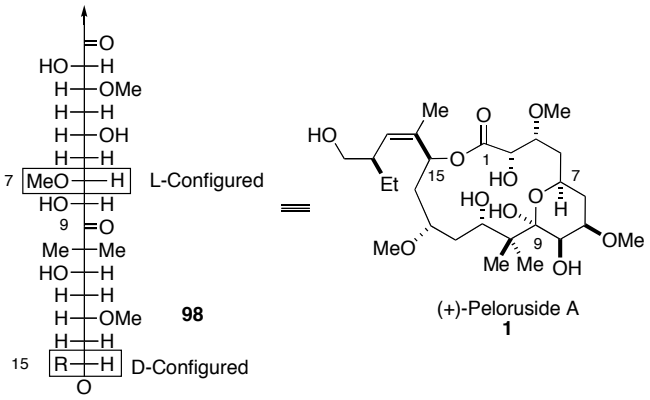



**Figure 1.15** Application of Celmer's rule to predict the configuration of peloruside A.

The synthesis plan involved macrolactonization of a seco acid **99** containing an elaborated pyran. This in turn would arise from a 1,5 anti aldol reaction between $C_{12}$–$C_{19}$ fragment **54** and $C_1$–$C_{11}$ fragment **100**. The initial disconnections were chosen to highlight 1,5-anti aldol methodology in the construction of the $C_{11}$-$C_{12}$ bond (Figure 1.16).[33]

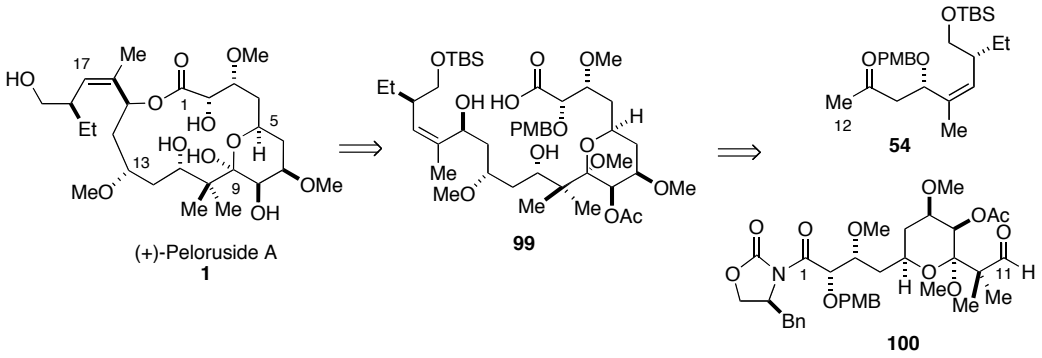


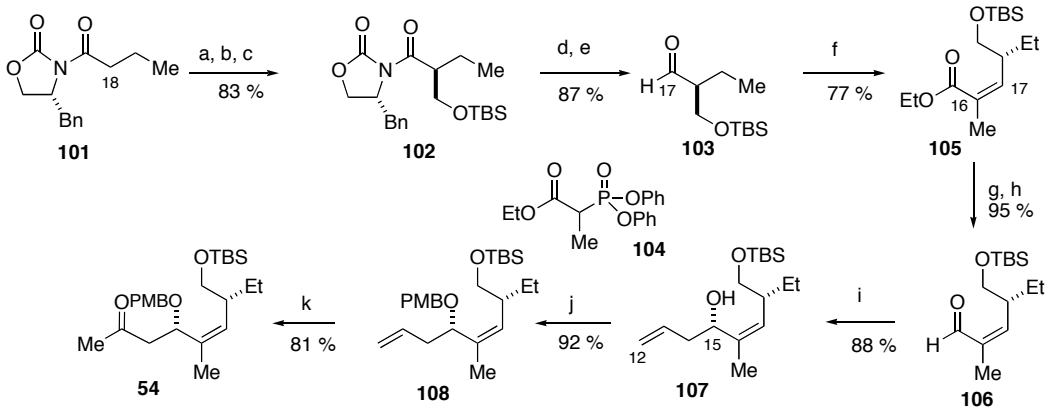

**Figure 1.16** The first generation synthesis plan.

(32) Cane, D. E.; Celmer, W. D.; Westley, W. *J. Am. Chem. Soc.* **1993**, *105*, 3594- 3600.

(33) Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T.; *J. Am. Chem. Soc.* **2003**, *125*, 10893-10898.

The synthesis of the $C_{12}$-$C_{19}$ fragment commenced with a titanium-mediated alkylation of butanoyl-loaded oxazolidinone **101** (Scheme 1.17).[34] The benzyl group was removed by hydrogenolysis and replaced with a TBS group to give compound **102** in 83% yield over 3 steps. This was then converted to aldehyde **103** in a 2-step sequence in 87% yield. This was subject to an Ando olefination with phosphonate **104** to give enoate **105** in 77% yield with a *Z/E* ratio > 20:1.[35] A 2-step sequence was used to convert enoate **105** into enal **106**. Enal **106** was subject to a Brown allylation to afford homoallylic alcohol **107**.[36] This alcohol was then protected as a PMB ether to give compound **108**. The PMB ether was chosen, as β-benzyloxy groups are effective controllers in 1,5-anti aldol reactions.[33,37] Finally the ketone was installed by a Wacker oxidation to afford $C_{12}$–$C_{19}$ fragment **54**.[38,1]

**Scheme 1.17**




a)$TiCl_4$, $Et_3N$, BOMCl,$CH_2Cl_2$ 0 °C; b) $H_2$, Pd/C, THF; c) TBSCl, im, DMF; d) $LiBH_4$, THF/$H_2O$; e) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$ -78 °C; f) NaH, **104**, THF at 0 °C then add **103** at -78 °C, then warm to 0 °C; g) DiBAlH, $CH_2Cl_2$, -78 °C; h) $MnO_2$, $CH_2Cl_2$; i) (+)$Ipc_2BAllyl$, $Et_2O$, -78 °C; j) NaH, PMBBr, DMF; k) $PdCl_2$, $Cu(OAc)_2$, $O_2$, DMF/$H_2O$

## The Moniz $C_{11}$ to $C_{12}$ Bond Construction

Concurrently, Dr. Moniz prepared a $C_1$–$C_{11}$ fragment **100** (Scheme 1.18). As this route was ultimately superseded by a different strategy, individual steps will not be described

(34) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215-8216.

(35) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411-8416.

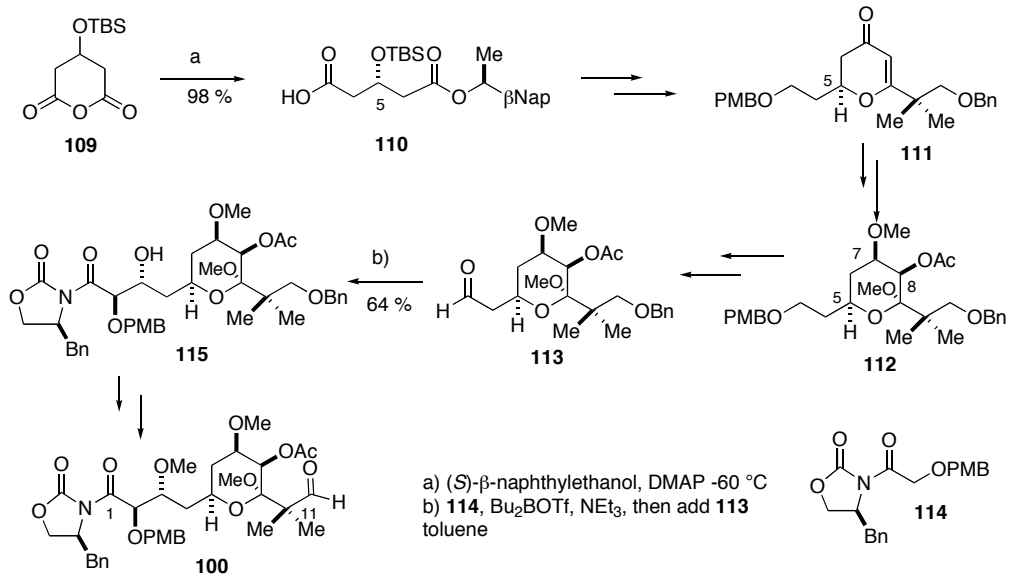
(36) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093

(37) Paterson, I.; Gibson, K. R.; Oballa, R. M.; *Tetrahedron Lett.* **1996**, *37*, 8585-8588.

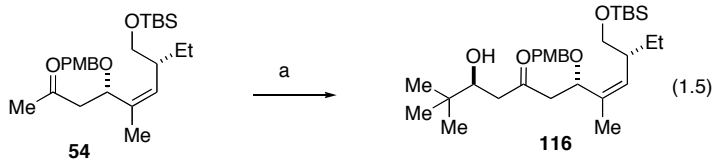
(38) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *17*, 2975-2976.

in detail. Meso anhydride **109** was desymmetrized using (*S*)-β-naphthylethanol **110**.[39] Pyranone **111** was prepared in 37% yield in 7 steps from compound **109**. Pyranone **111** was elaborated to compound **112** in a 5-step sequence in 54% yield. The $C_2$–$C_3$ bond was formed by elaboration of compound **112** to the corresponding aldehyde **113** followed by a glycolate aldol with oxazolidinone **114** to afford aldol adduct **115**. 3 more steps served to elaborate this aldol adduct to the final $C_1$–$C_{11}$ fragment **100**.

**Scheme 1.18**



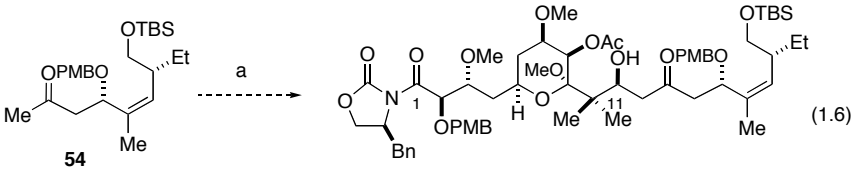

Dr. Moniz then investigated an aldol reaction of $C_{12}$-$C_{19}$ fragment **54** with pivaldehyde as a model system (Equation 1.5). The dibutyl boron triflate mediated reaction proceeded in good yield to give aldol adduct **116** with superb diastereoselectivity.




a) $Bu_2BOTf$, $iPr_2NEt$, $Et_2O$, -78 °C, then *t*BuCHO at -78 °C

(39) Theisen, P. D.; Heathcock, C. H.; *J. Org. Chem.* **1988**, *53*, 2374- 2378.

Unfortunately, the fragment coupling between **54** and **100** failed to give any product under the same conditions, or using LDA to enolize fragment **54** (Equation 1.6).

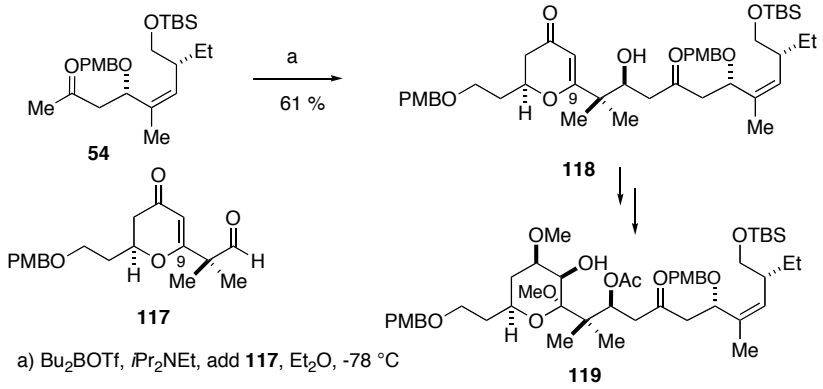



(1.6)

a) $Bu_2BOTf$, $iPr_2NEt$, $Et_2O$, -78 °C, then **100**, or LDA, THF, then **100**

Dr. Moniz speculated that the steric bulk of the protected hydroxyls at $C_7$ and $C_8$ led to the low reactivity in fragment **100**. Accordingly, he attempted the aldol reaction with less sterically hindered compound **117**, derived from pyranone intermediate **111**. This underwent the desired aldol reaction in acceptable yield with superb diastereoselectivity (Scheme 1.19). The increase in reactivity was attributed to the lower steric demand around the $C_{11}$ aldehyde by having an $sp^2$ centre at $C_9$. Aldol adduct **118** was then elaborated to intermediate **119** in a sequence that involved an Evans–Tishchenko reduction, followed by a Luche reduction, directed epoxidation and methanolysis.

**Scheme 1.19**



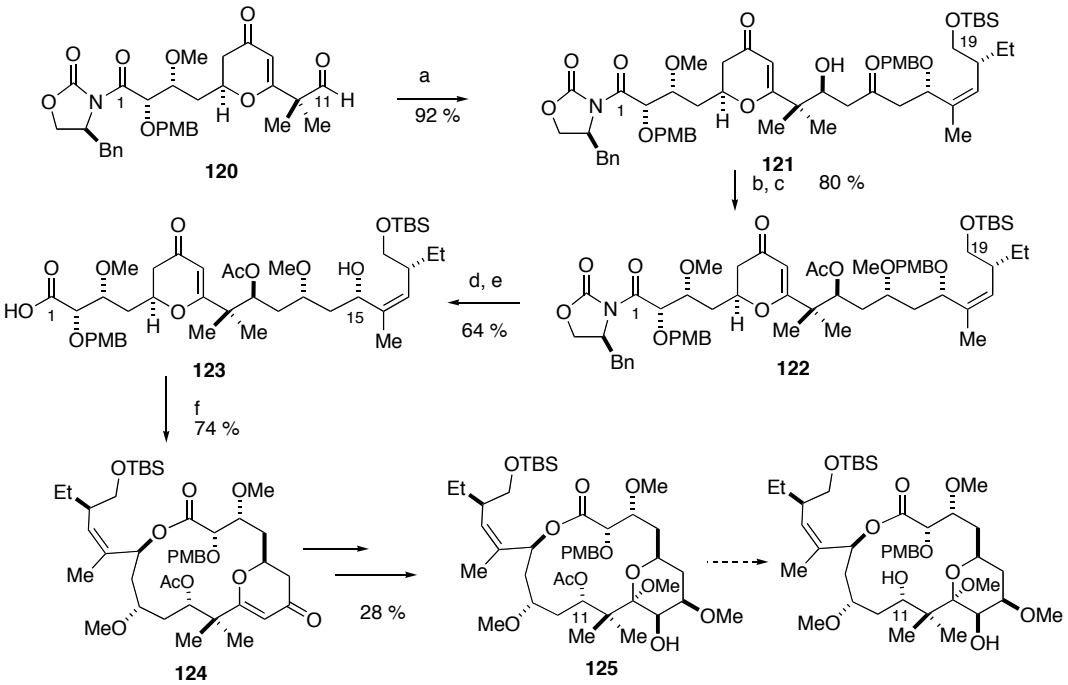

a) $Bu_2BOTf$, $iPr_2NEt$, add **117**, $Et_2O$, -78 °C

Dr. Moniz's key contributions to the project involved the synthesis of $C_{12}$–$C_{19}$ fragment **54** and the demonstration that this fragment could undergo highly selective 1,5-anti aldol reactions. A very important contribution was the observation that the $C_{11}$–$C_{12}$ bond construction was sensitive to sterics, and that this reaction could proceed with a β-vinylogous keto aldehyde in substrate **117**.

**The Reichelt Approach**

The project was taken over by Dr. Andreas Reichelt. Dr. Reichelt preformed the same bond construction on more elaborate pyranone **120**, using a $C_{19}$ TBDPS analogue of ketone **54**. Aldol adduct **121** was elaborated by Evans–Tishchenko reduction and methylation to yield peloruside A backbone **122** (Scheme 1.20). Unfortunately elaboration of the pyranone was not possible at this stage as concomitant cleavage of the oxazolidinone was observed. It was decided to conduct pyranone elaboration after the macrolactonization, which was the strategy used by Taylor.[17,40]

**Scheme 1.20**



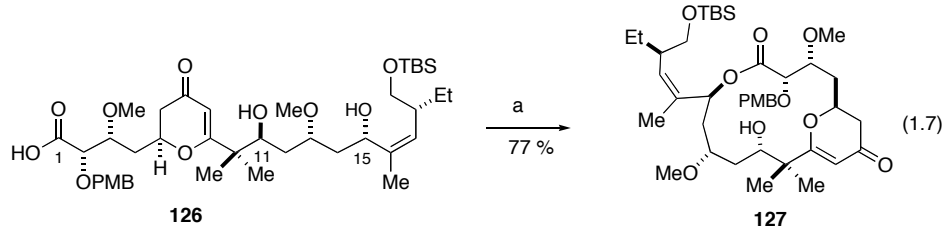

a) $Bu_2BOTf$, **54,** $iPr_2NEt$, then **120** toluene, -78 °C b) MeCHO, $SmI_2$, THF c) $Me_3OBF_4$, Proton Sponge
d) DDQ, $CH_3CN$ e) LiOH, $H_2O_2$, THF f) 2,4,6-trichlorobenzoyl chloride, DMAP, benzene, rt

The PMB group at the $C_{15}$ hydroxyl could be selectively cleaved in the presence of the $C_2$ PMB protection, followed by oxazolidinone cleavage to yield seco acid **123**. Yamaguchi macrolactonization gave pyranone **124**, which was elaborated in a 4-step sequence to

(40) The synthesis of Taylor had not been disclosed at this point.

protected peloruside A **125**. Unfortunately, the acetate group on the $C_{11}$ hydroxyl, originating in the Evans–Tishchenko reduction could not be cleaved.

The acetate group could be removed at an earlier stage to generate seco acid **126** with free hydroxyl groups at both $C_{11}$ and $C_{15}$. This did undergo a site selective Yamaguchi reaction (Equation 1.7) to yield **127**. Unfortunately elaboration of the pyranone according to the method that worked on **124** was unsuccessful on this intermediate.




**126** **127**

a) 2,4,6-trichlorobenzoyl chloride, DMAP, benzene, rt

At this stage it was decided to revise the strategy for the synthesis of the molecule given the difficulties in elaborating the pyranone at the late stage. An important finding from this work was that the $C_{11}$–$C_{12}$ bond could be constructed with an oxazolidinone at $C_1$.

**Second Generation Reichelt Approach**

The second generation strategy involved cyclization of a pyran containing seco acid **128**, arising from a non- pyran containing piece **129**, which in turn would be assembled from $C_1$–$C_6$ fragment **130**, $C_7$–$C_{11}$ fragment **131** or **132** and $C_{12}$–$C_{19}$ fragment **133** (Figure 1.17). It was anticipated constructing the $C_{11}$–$C_{12}$ bond on a non pyran-containing piece would be possible because of lowered steric demand at a $C_{11}$ aldehyde in the absence of the pyran. The formation of the pyran would occur through cyclization of a $C_5$ alcohol onto the $C_9$ ketone, and would precede the macrocyclization, but would come after the $C_{11}$–$C_{12}$ bond construction. Accordingly, an orthogonal group would be employed to protect the $C_9$ hydroxyl. This would be removed and the $C_9$ alcohol oxidized before pyran formation. The BOM group in fragment **131** or the DMB group in **132** were envisioned as such protecting groups. Fragments **131** and **132** both contain latent aldehydes at $C_7$ and

$C_{11}$. Fragment **131** was designed for a convergent strategy, where the $C_6$–$C_7$ bond construction would precede the $C_{11}$–$C_{12}$ bond construction, with a labile TES group at $C_{11}$ being envisioned to be removed after the first fragment coupling to enable $C_{11}$ oxidation to the aldehyde for the second fragment coupling. Fragment **132** was designed for a less convergent strategy, where $C_{11}$–$C_{12}$ bond construction would occur first. The use of a monosubstituted olefin was to ensure that oxidative cleavage could then take place in the presence of the trisubstituted $C_{16}$–$C_{17}$ olefin. The protecting group strategy employed at the $C_5$ alcohol, would vary according to the fragment coupling strategy employed, however one option would employ a TBS group, so in anticipation of a selective deprotection at that position, the a TBDPS group was employed to protect the $C_{19}$ alcohol in fragment **133**.

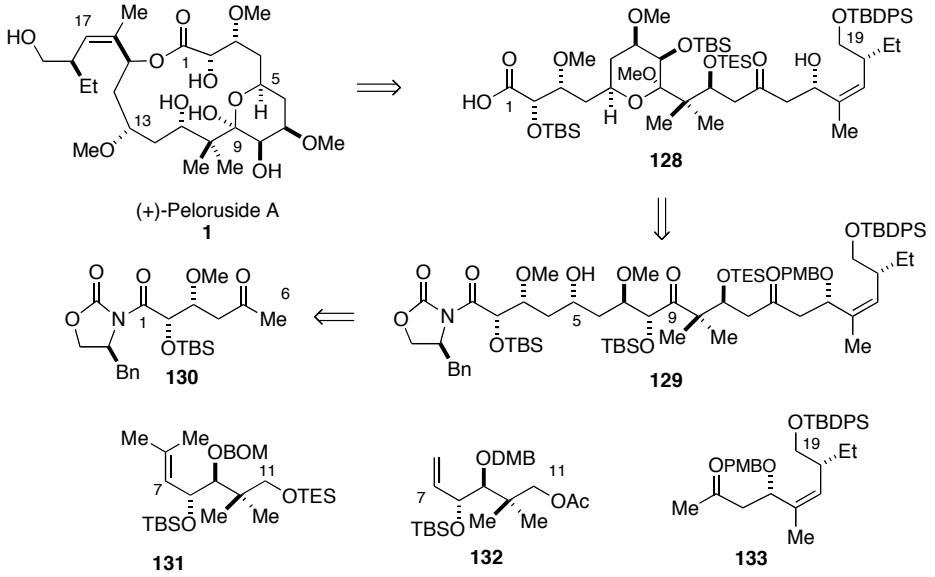
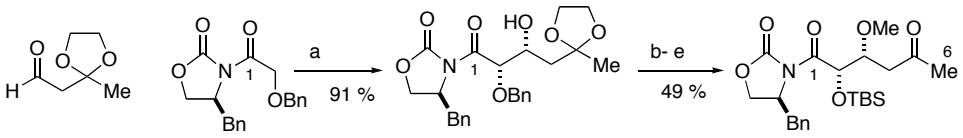



**Figure 1.17** Second generation approach.

The synthesis of the $C_1$–$C_6$ fragment involved a glycolate aldol reaction of oxazolidinone **134** into aldehyde **135**, followed by protecting group manipulations on aldol adduct **136** to afford fragment **130** in 4 steps (Scheme 1.21).

**Scheme 1.21**



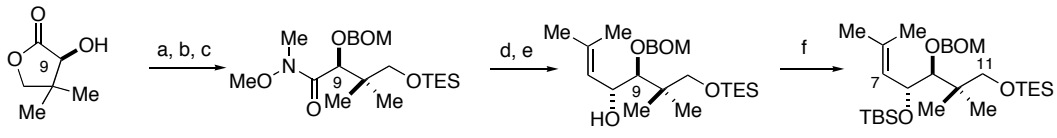
**135** **134** **136** **130**

a) **135**, $Bu_2BOTf$, $iPr_2NEt$, $CH_2Cl_2$; b) $Me_3OBF_4$, Proton Sponge ®; c) $H_2$, $Pd(OH)_2$, THF;
d) TBSOTf, 2,6-lutidine, $CH_2Cl_2$; e) PPTS, wet acetone

The configuration at $C_9$ of fragments **131** and **132** is ultimately inconsequential as $C_9$ is oxidized to the ketone oxidation state at later stages in the synthesis. However, the relative configuration of the $C_8$ and $C_9$ positions has a great deal of importance on the $C_6$–$C_7$ bond construction. The use of an anti arrangement of $C_8$ and $C_9$ was chosen based on the results of an extensive series of investigations into aldol reactions into α,β-oxygenated aldehydes conducted in our group by Dr. Sarah Siska and Dr. Victor Cee.[41] The implications of this study to our strategy will be discussed in more detail in the summary on Dr. Dennie Welch's work.

Synthesis of $C_7$–$C_{11}$ fragment **131** proceeded in 6 steps from (*S*)-pantolactone **137** (Scheme 1.22). BOM protection, opening of the lactone with Weinreb amine and TES protection of the resultant alcohol proceeded in high yield to afford Weinreb amide **138** in high yield. Addition of the Grignard reagent derived from 1-bromo-2-methylprop-1-ene and chelate controlled reduction with $Zn(BH_4)_2$ proceeded in modest yield to afford alcohol **139**. The choice of the highly substituted Grignard reagent was based on slowing competing 1,4 hydride reduction in the reduction step. Protection afforded fragment **131**.

**Scheme 1.22**



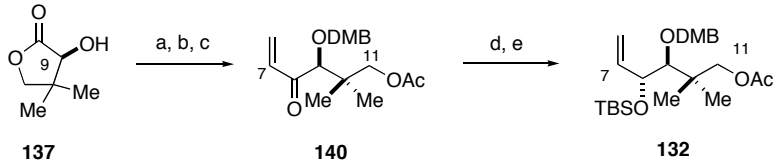
**137** **138** **139** **131**

a) BOMCl, $iPr_2NEt$, TBAI, $CH_2Cl_2$; b) MeONHMe•HCl, $AlMe_3$ $CH_2Cl_2$ ; c) TESCl, im, $CH_2Cl_2$
d) $Me_2C$=CHMgBr, THF; e) $Zn(BH_4)_2$ , $Et_2O$; f) TBSCl, im, DMF

(41) Evans, D. A. Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433- 9441.

The $C_7$–$C_{11}$ fragment **132** was prepared by DMB protection of (*S*)-pantolactone, followed by monoaddition of vinyllithium and acetylation of the resultant primary alcohol giving enone **140**. Chelate controlled reduction, and TBS protection gave fragment **132** (Scheme 1.23).

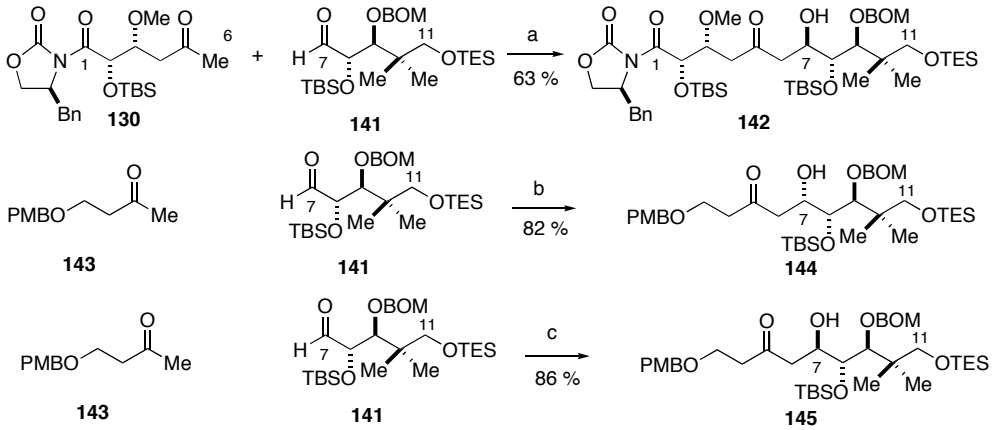
**Scheme 1.23**




a) DMBOC(=NH)$CF_3$, CSA, $CH_2Cl_2$; b) $H_2C$=CLi, $Et_2O$; c) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$;
d) $Zn(BH_4)_2$, $Et_2O$; e) TBSOTf, 2,6 lutidine, $CH_2Cl_2$;

Initial fragment coupling investigations were carried out with ketone **130** and aldehyde **141**, derived from ozonolysis of fragment **131** (Scheme 1.24). Unfortunately enolization of **130** with 9-BBN triflate, the reagent used in the Cee and Siska studies did not work. Decomposition was attributed to the sensitivity of the $C_2$ OTBS group. Use of dibutylboron triflate gave resulted in the formation of aldol adduct **142** but with only 2:1 diastereoselection the correct way. An investigation using model methyl ketone **143** showed that dicyclohexylboryl enolates gave predominantly the incorrect configuration at $C_7$ in compound **144** with a dr of 4:1.

**Scheme 1.24**

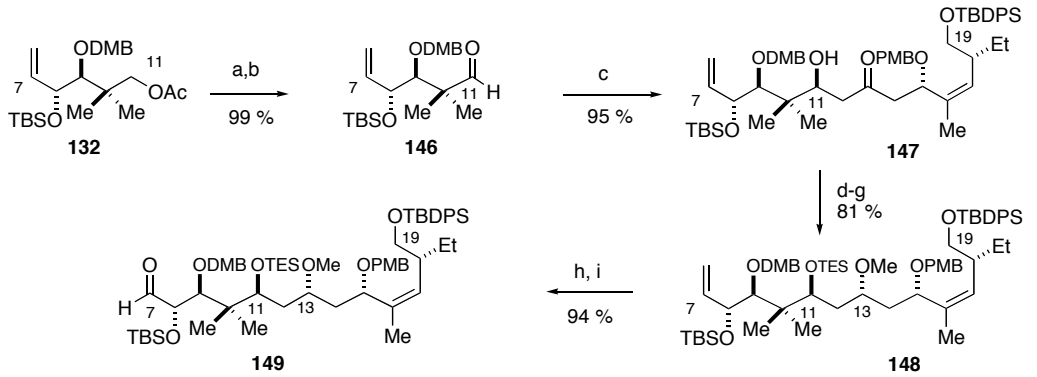



a) $Bu_2BOTf$, *i*$Pr_2NEt$, toluene, -78 °C; b) $Cy_2BCl$, $Et_3N$, $CH_2Cl_2$ -78 °C; c) LDA, THF, -78 °C

Use of LDA with **143** gave the desired stereochemistry at $C_7$ in compound **145** with a selectivity of > 95:5. Unfortunately fragment **130** was not stable to LDA, undergoing decomposition due to the electrophilicity of the $C_1$ carboxylate. Unfortunately efforts to elaborate compound **145** to a later intermediate were stymied by issues with the $C_3$ PMB protecting group.

At this point, the decision was made to investigate the $C_{11}$-$C_{12}$ bond construction (Scheme 1.25). The crucial $C_{11}$-$C_{12}$ bond construction proceeded in excellent yield and diastereoselectivity (95%, dr > 95:5) between **133** and aldehyde **146**, derived from fragment **132**. Aldol adduct **147** was obtained in high yield despite the fact that $C_9$ was in alcohol oxidation state. Subsequent Evans–Tishchenko reaction relayed the stereochemistry from $C_{11}$ to $C_{13}$, followed by methylation of the $C_{13}$ alcohol, acetate removal at $C_{11}$ and TES protection at $C_{11}$ afforded compound **148**, which could be converted to $C_7$-$C_{19}$ aldehyde **149** in a 2 step sequence.

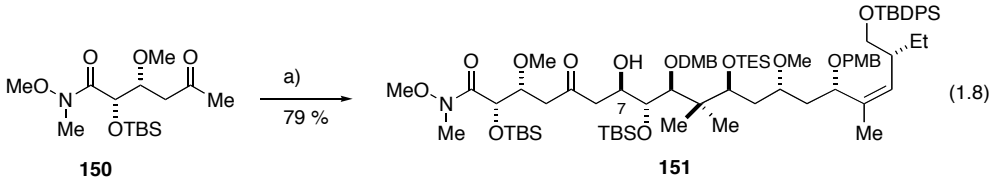
**Scheme 1.25**




a) EtMgCl, THF; b) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$ c) **133,** $Cy_2BCl$, $iPr_2NEt$, then **146** $Et_2O$, -78 °C
d) MeCHO, $SmI_2$ THF, -10 °C; e) $Me_3OBF_4$, proton sponge, $CH_2Cl_2$ ; f) DiBAlH, $CH_2Cl_2$, -30 °C,
g) TESOTf, 2,6-lutidine$CH_2Cl_2$, -78 °C; h) $OsO_4$, NMO, THF/acetone/ pH 7; i) $NaIO_4$, THF/ pH 7;

Given the results obtained in Scheme 1.24, a lithium aldol reaction was used to construct the $C_6$-$C_7$ bond. Since **133** was decomposed by LDA, the more resistant Weinreb amide **150** was synthesized and employed. The key fragment coupling proceeded in good yield, but with excellent stereoselectivity (79%, dr 95:5) to afford peloruside A backbone **151**

(Equation 1.8). Unfortunately 10 equivalents of **133** were needed, as self-condensation was still somewhat operative. At this point, Dr. Dennie Welch joined the project, and was tasked with investigating the $C_6$–$C_7$ bond construction.




a) LDA, THF, then **149**, -78 °C;

## IV. The Welch Synthesis

### Discovery of Boron Ligand Effects in the $C_6$ to $C_7$ Bond Construction

Dr. Welch began a systematic investigation of boron aldol reactions to construct the $C_6$-$C_7$ bond. It was hoped that boron aldol reactions would allow stoichiometric use of the C-$_1$-$C_6$ fragment. A decision was also made to use compounds with a group at $C_1$ that could be more readily cleaved to the carboxylic acid. Accordingly compound **130** was revisited and **152**, shown in Figure **1.18** were prepared based on the route shown in Scheme **1.26**.

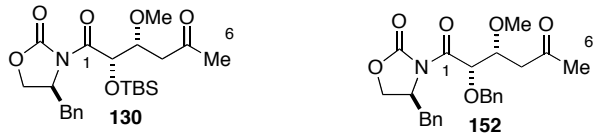
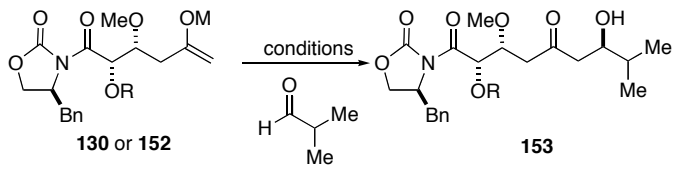



**Figure 1.18** Methyl ketones utilized by Dr. Welch.

The intrinsic diastereoselectivity of this reaction was probed using isobutyraldehyde (Table 1.1) yielding aldol adducts **153**. It should be noted this reaction did not have a wide degree of sensitivity to the identity of the boron reagent, although 9-BBN appeared to be slightly inferior.

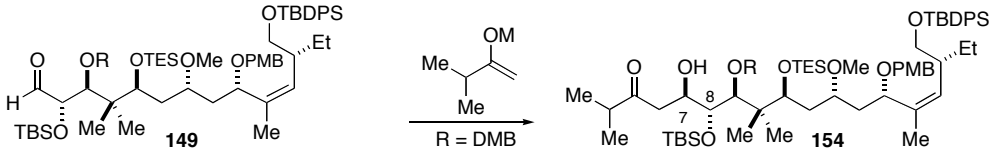
**Table 1.1**[42]




| entry | R | M | solvent | dr |
|---|---|---|---|---|
| 1 | Bn | 9-BBN | $CH_2Cl_2$ | 2.0 : 1 |
| 2 | Bn | 9-BBN | toluene | 2.0 : 1 |
| 3 | Bn | $Bu_2B$ | toluene | 2.8 : 1 |
| 4 | Bn | $Cy_2B$ | toluene | 3.0 : 1 |
| 5 | TBS | 9-BBN | toluene | N.R. |
| 6 | TBS | $Cy_2B$ | toluene | 2.0 : 1 |

The behavior of model enolates derived from methyl isobutyl ketone with aldehyde **149** was also studied (table 1.2). The lithium enolate gave a very high diastereoselectivity for **154** as would be expected given the fragment coupling shown in equation 1.8. The low diastereoselectivity with the 9-BBN enolate is noteworthy given results that will be reported in Chapter 2 and also surprising as the Cee and Siska results had high selectivity with 9-BBN enolates on anti α,β oxygenated aldehydes.[41]

**Table 1.2** Investigation intrinsic diastereoselectivity of **149**.[42]

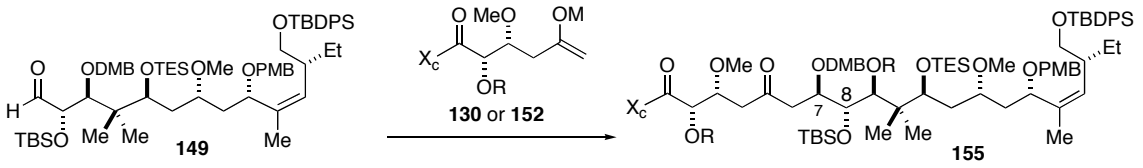



| entry | M | 7,8-*anti* : 7,8-*syn* |
|---|---|---|
| 1 | $Cy_2B$ | <5 : 95 |
| 2 | 9-BBN | 1.0 : 1.2 |
| 3 | Li | >95 : 5 |

Finally, ketones **152** and **153** were allowed to react with $C_7$-$C_{19}$ fragment **149** under a variety of enolization conditions to give adduct **155**. The lithium enolates of compound **152** and **153** are not stable, undergoing a destructive self-cyclization, so this study was limited to Boron enolates (Table 1.3**)**.

(42) The following table is reproduced with permission from Dr. Dennie Welch.

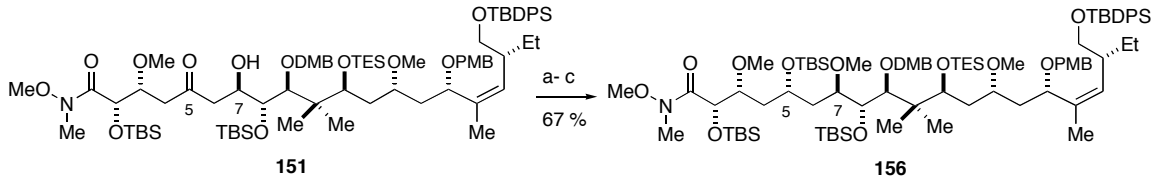
**Table 1.3** Fragment coupling Investigation.[42]




| entry | R | M | 7,8-*anti* : 7,8-*syn* |
|---|---|---|---|
| 1 | Bn | 9-BBN | 4 : 1 |
| 2 | Bn | $Cy_2B$ | 1 : 10 |
| 3 | TBS | $Cy_2B$ | <5 : 95 |
| 4 | TBS | $Bu_2B$ | 1 : 2 |

It can be seen from the above results that the diastereoselectivity of these aldol reactions is highly dependant on the identity of the Boron species used with the best result being 9-BBN triflate mediated enolization of **152**. Unfortunately, 9-BBN triflate did not result in a successful enolization of **130** with a TBS group at the $C_2$ alcohol, and it was felt at the time that a benzyl protection at this position would be incompatible with global deprotection because of the $C_{16}$-$C_{17}$ alkene.[43] Accordingly the decision was made to the conditions that produced **151**. Elaboration of **151** was carried out via 1,3 anti reduction mediated by $Me_4N$ $HB(OAc)_3$ in greater than 10:1 dr,[44] followed by selective TBS protection of the $C_5$ alcohol and methylation of the $C_7$ alcohol to product fully protected peloruside A backbone **156** (Scheme 1.26).

**Scheme 1.26**




a) $Me_4N$ $HB(OAc)_3$ , AcOH. $CH_3CN$, -30 °C; b) TBSCl, im, DMF; c) $Me_3OBF_4$, Proton Sponge ®, $CH_2Cl_2$.

(43) This was prior to the hydrogenolysis of the $C_{19}$ benzyloxy group reported by Ghosh. It is unclear if a benzyl group on the much more sterically hindered $C_2$ position could be subject to selective hydrogenolysis in the presence of the $C_{16}$-$C_{17}$ alkene.

(44) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560- 3578.

At this point, Dr. Welch decided to investigate a switch in the order pyran formation and macrocyclization. Dr. Welch felt there was literature precedent that suggested that formation of the pyran adjacent to the geminal dimethyl group at $C_{10}$ that was planned in synthesis plan intermediate **128** might be difficult.[45] Accordingly Dr. Welch decided to attempt a macrocyclization of a linear seco acid **157** followed by pyran formation during the global deprotection. This work was conceived prior to Ghosh's disclosure of such a strategy. Since Dr. Welch was working with material protected with a DMB group on the alcohol at $C_9$ and a PMB group on the alcohol at $C_{15}$, removal of the $C_{15}$ alcohol-protecting group would also result in the deprotection of the alcohol at $C_9$. A solution to avoid a protecting group swap at $C_9$ would be to attempt a selective macrocyclization on seco acid **157** containing free alcohols at both $C_9$ and $C_{15}$. This was deemed to be feasible given the steric congestion around $C_9$. Oxidation of $C_9$ on macrolactone **158** to the ketone would precede pyran formation at the global deprotection. (Figure 1.19)

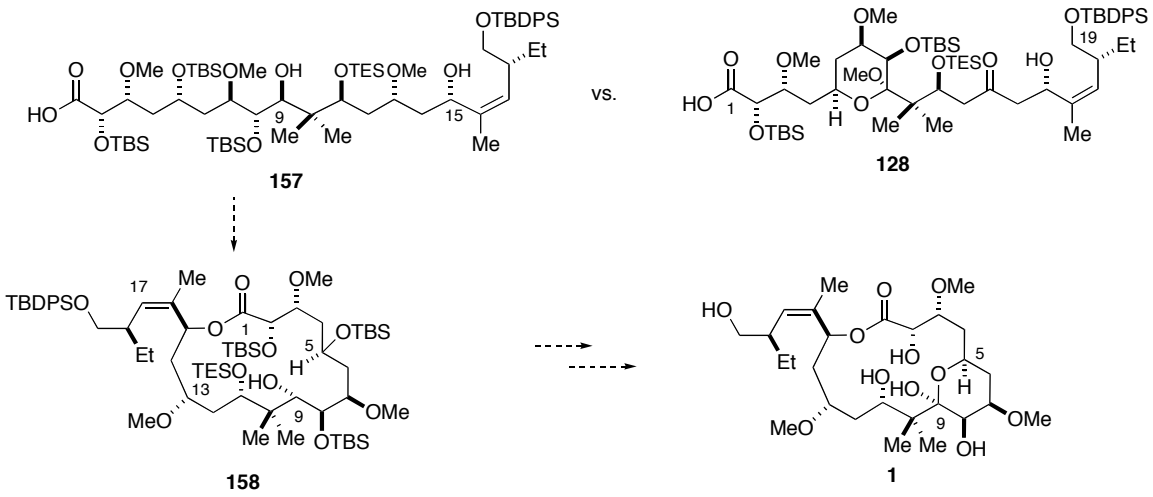



**Figure 1.19** Revised cyclization order.

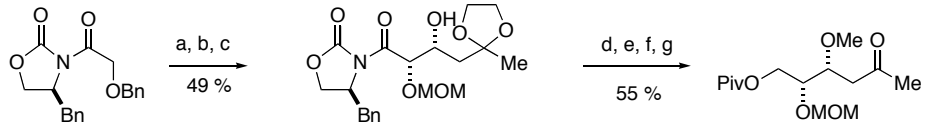
Dr. Welch was able to elaborate compound **156** to seco acid **157**. Unfortunately, this compound proved to be unstable, attributable to lability of the TBS protecting group on

(45) Keck, G. E.; Yu, T.; McLaws, M. D.; *J. Org. Chem.* **2005**, *70*, 2543- 2550.

the $C_2$ alcohol. Lability of OTBS groups α to carboxylic acids has been observed during synthesis efforts towards peloruside[46], tedanolide,[47] and psymberin.[48]

Dr. Welch then decided to follow the precedent of DeBrabander and Taylor and employ a MOM protecting group at the $C_2$ alcohol. The supply of the $C_7$–$C_{19}$ aldehyde **149** was growing short, and Dr. Welch wanted to test the feasibility of the pyran formation following macrolactonization without having to do another scale up. Accordingly, a Piv ester was chosen to protect the $C_1$ terminus of the $C_1$–$C_6$ fragment since this would anticipated to be resistant to self-condensation, resulting in a stable lithium enolate and hopefully a reliable fragment coupling. The required $C_1$–$C_6$ fragment **159** was prepared by in 7 steps from oxazolidinone **134** by way of aldol adduct **160** (Scheme 1.27)

**Scheme 1.27**




**134** **160** **159**

a) $Pd(OH)_2/C$, $H_2$, EtOAc; b) MOMCl, TBAI, *i*-$Pr_2NEt$, $CH_2Cl_2$; c) $Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$ then **135**, -78 °C; d) $Me_3OBF_4$, proton sponge®, $CH_2Cl_2$; e) $LiBH_4$, MeOH, THF, 0 °C f) PivCl, DMAP, $Et_3N$, $CH_2Cl_2$; g) PPTS, acetone, $H_2O$, reflux.

Revised $C_1$-$C_6$ fragment **159** was employed in the $C_6$-$C_7$ bond construction with high diastereoselectivity to give aldol adduct **160**.[49] Elaboration by 1,3-anti reduction, followed by $C_5$ silylation and $C_7$ methylation afforded peloruside A backbone **161**. This was converted into seco acid **162** in a 4-step sequence (Scheme 1.28).

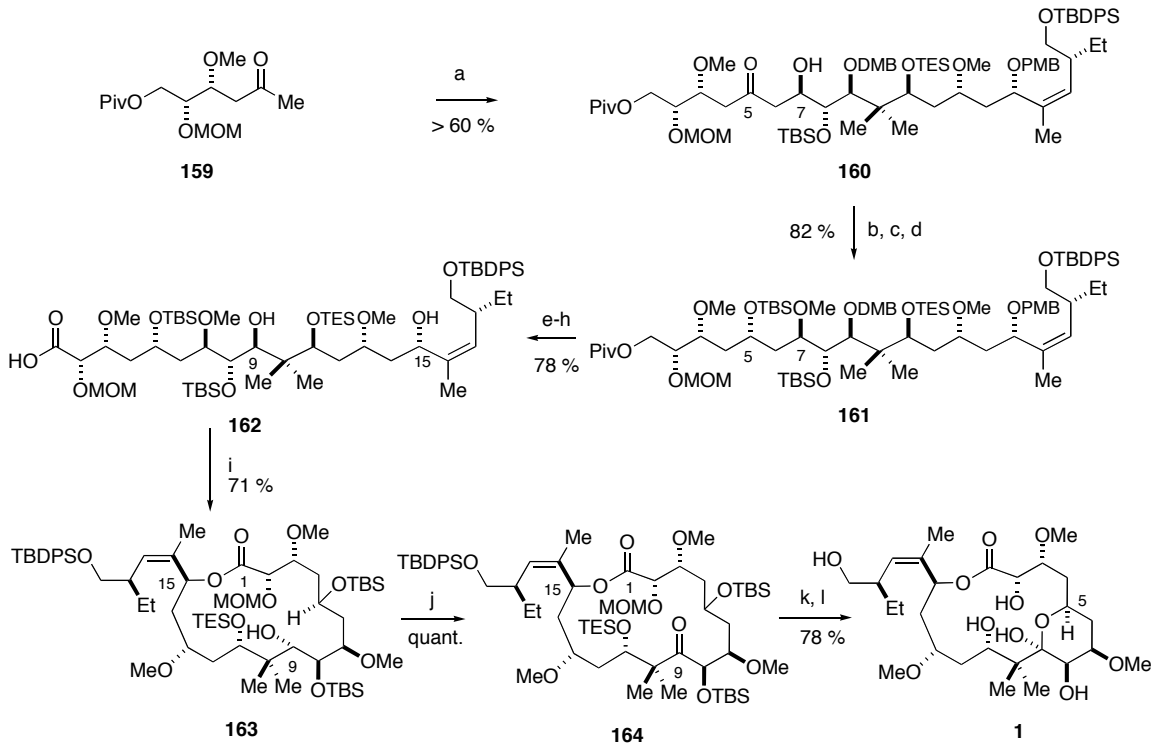
(46) Zheng, J. Ph.D. Thesis, University of Pennsylvania, **2003**.

(47) Hassfeld, J.; Eggert, U.; Kalesse, M. *Synthesis*, **2005**, *7*, 1183- 1199.

(48) Kiren, S.; Williams, L. J. *Org. Lett.* **2005**, *7*, 2905- 2908.

(49) The reaction was complicated by up to 40% $E_1CB$ elimination of methanol from $C_3$, producing an inseparable olefin. This was removed by treatment with $OsO_4$ after the 1,3 anti reduction step, yielding a readily separable tetraol.

**Scheme 1.28**




a) LDA, THF, then **149** -78 °C; b) $NaHB(OAc)_3$, AcOH, $CH_3CN$, -30 °C, then $OsO_4$, NMO (see text); c)TBSCl, im, DMF; d)$Me_3OBF_4$, Proton Sponge ®, $CH_2Cl_2$; e) DiBAlH, tol, -78 °C; f) DMP, py, $CH_2Cl_2$, 10 °C g) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH, THF, $NaH_2PO_4$; h) DDQ, $CH_2Cl_2$, pH 7 buffer; i) 2, 4, 6-trichlorobenzoyl chloride, *i*-$Pr_2NEt$, THF, then DMAP, tol 60 °C; j) DMP, py, $CH_2Cl_2$, 0 °C; k)HF•py, py, THF, l) 4N HCl, THF

The crucial macrolactonization to **163** proceeded in 71% yield under Yamaguchi conditions. The reaction was site selective for macrocyclization onto the $C_{15}$ alcohol despite the presence of a free alcohol at $C_9$. This important result showed that the linear seco acid could be cyclized. Oxidation of the $C_9$ alcohol to the ketone with Dess- Martin periodinane proceeded uneventfully to give fully protected peloruside A **164**. Exposure of macrolactone **164** to 4N HCl did not result in the formation of peloruside A, as it appeared that the TBDPS group was still on. Exposure of TBDPS macrolactone to HF-Py, py, followed by 4N HCl did result in the synthesis of peloruside A, validating the concept of forming the pyran after macrocyclization.[50]

(50) Dr. Welch completed this synthesis on June 4th 2007, which preceded Ghosh's publication of a similar strategy on February 5th 2008.

Dr. Welch's work resulted in the validation of the strategy of cyclization of a linear seco acid, showed that a site selective macrolactonization was feasible, and showed that boron ligand effects influenced the diastereoselectivity of the $C_6$–$C_7$ bond construction. This first generation synthesis had a longest linear sequence of 31 steps, and it was readily appreciated that there was room for improvement since the strategy of late pyran formation had been conducted on material that originally had a protecting group strategy for another purpose.

**The Second Generation Welch Retrosynthesis**

Critical examination of the first generation synthesis showed several areas that detracted from the overall efficiency. Synthesis of the $C_{12}$–$C_{19}$ fragment **133** or **54** requires 12 steps, while synthesis of the $C_7$–$C_{11}$ fragment **131** is 6 steps and the $C_1$–$C_6$ fragment **159** also 6 steps. By placing the $C_{11}$–$C_{12}$ bond construction before the $C_6$–$C_7$ bond construction, the $C_{11}$–$C_{21}$ fragment synthesis is within the longest linear sequence, impacting the overall convergency of the synthesis. The problems encountered in the $C_6$–$C_7$ bond construction necessitated the use of a $C_1$–$C_6$ fragment **159** with the $C_1$ terminus in an alcohol rather than carboxylate oxidation state and represented an obvious target for improvement. Targeting a MOM group to protect the alcohol at $C_2$ while $C_1$ was in the carboxylate oxidations state would provide new substrates that had not been successful with $C_2$ OTBS fragment **130** or $C_2$ OBn fragment **152**. A final improvement in efficiency was targeted in when the ketone oxidation state was introduced at $C_9$. It was anticipated that having a ketone at $C_9$ could actually enhance the reactivity of a $C_{11}$ aldehyde in the $C_{11}$–$C_{12}$ bond construction. In that case, the alcohols at $C_9$ and $C_{11}$ could be protected with protecting groups that could be cleaved under the same conditions, and both alcohols could be oxidized concurrently.

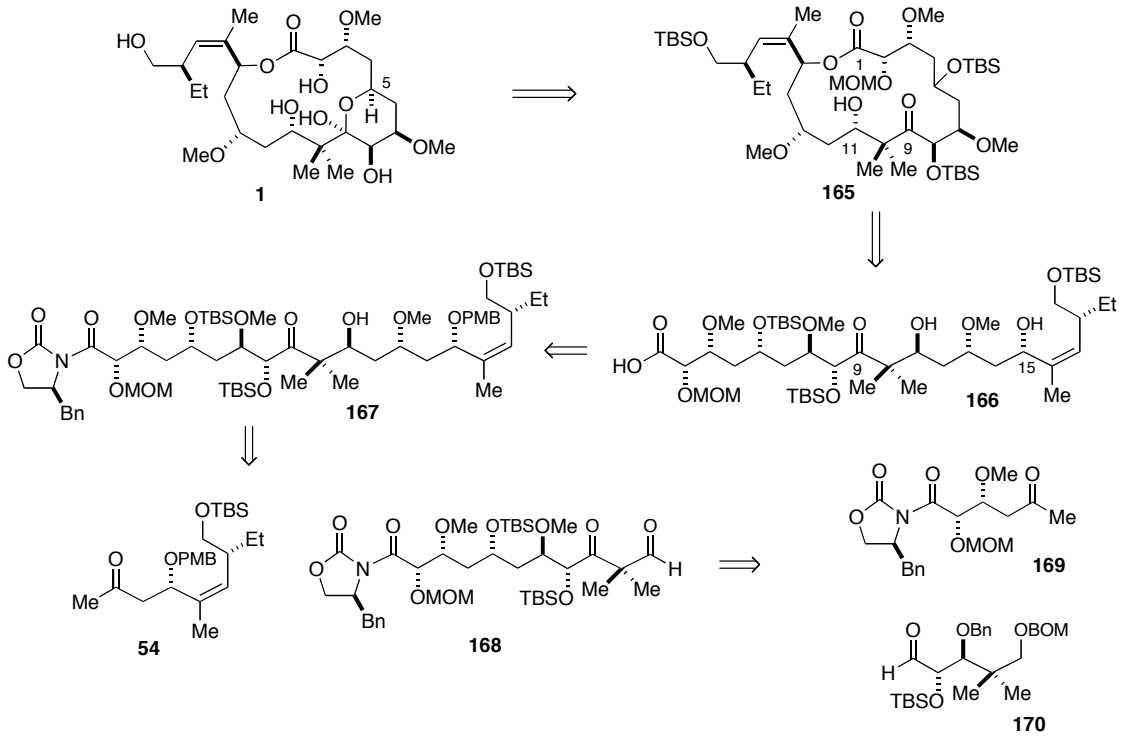



**Figure 1.20** New synthesis plan devised by Dr. Welch.

This would enable a further 2 steps to be cut from the synthesis. It should be noted an early oxidation of $C_9$ would result in the requirement for directed reduction of the $C_{13}$ ketone in the presence of the $C_9$ ketone. It was anticipated that the $C_{10}$ geminal dimethyl group would decrease the reactivity of the $C_9$ ketone such that this reaction could be achieved. These considerations resulted in the synthesis plan shown in Figure 1.20 with a projected longest linear sequence of 23 steps.

Peloruside A would arise from macrolactone **165**, which bears a free hydroxyl at $C_{11}$. This would arise from the cyclization of linear seco acid **166** with $C_9$ already at the ketone oxidation state. Seco acid **166** would be synthesized from peloruside A backbone **167**, which in turn would arise from an aldol reaction between known fragment **54** (see Scheme 1.17) and β-keto aldehyde **168**. Compound **168** would be prepared from ketone **169**, which bears similarity to known intermediates **130** (see Scheme 1.21), and aldehyde

**170** which would be made in a similar method to compound **131** (see Scheme 1.22). The implementation of this strategy will be described in the next chapter.

# *Chapter 2*

## Completion of the Total Synthesis of Peloruside A[1,2]

### I. Assembly of the Carbon Backbone of Peloruside A

The second generation synthesis plan for peloruside A, **1**, developed by Dr. Welch in the previous chapter, targeted a linear seco acid **2** arising from a $C_6$–$C_7$ bond construction that preceded the $C_{11}$–$C_{12}$ bond construction (Figure 2.1). The seco acid contains 1,3-anti relationships between $C_5$ and $C_7$ and $C_{11}$ and $C_{13}$ that may arise from 1,3-anti reductions. Also, 1,5-anti relationships between $C_3$ and $C_7$ and $C_{11}$ and $C_{15}$ are apparent that may arise from 1,5-anti aldol reactions. The $C_6$–$C_7$ bond construction would arise between $C_1$–$C_6$ fragment **3** and $C_7$–$C_{11}$ fragment **4**. These fragments bear close resemblance to fragments prepared by Dr. Reichelt and Dr. Welch as described in the preceding chapter. The $C_{11}$–$C_{12}$ bond construction would involve $C_{12}$–$C_{19}$ fragment **5**, which is known from Dr. Moniz's work.

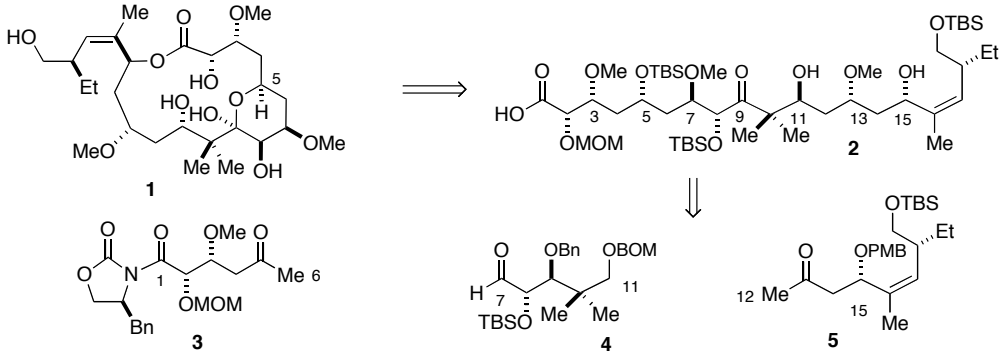



**Figure 2.1** Fragments targeted in this work.

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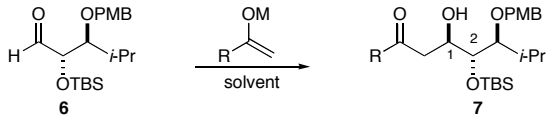
(1) Reproduced in part with permission from Evans, D. A.; Welch, D. S.; Speed, A. W. H.; Moniz, G. A.; Reichelt, A.; Ho, S. "An Aldol-Based Synthesis of (+)-Peloruside A, A Potent Microtuble Stabilizing Agent" *J. Am. Chem. Soc.* **2009**, *131*, 3840-3841. © 2009 by The American Chemical Society.

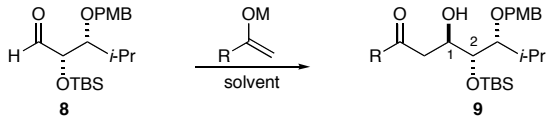
(2) Much of the work described in this chapter was conducted in conjunction with Dr. Dennie Welch, and Mr. Stephen Ho, an undergraduate student in our lab. This is noted accordingly were applicable.

I joined the project shortly after Dr. Welch began work on this second generation strategy. My initial task was to synthesize the new $C_1$–$C_6$ fragment via an adaptation of the previous work done by Dr. Welch and Dr. Reichelt. I then proceeded to investigate the $C_6$–$C_7$ bond construction with aldehydes prepared by Dr. Welch. A strong precedent for this bond construction may be found in the work of Dr. Sarah Siska and Dr. Victor Cee.[3] The results most pertinent to the peloruside A bond construction are shown in table 2.1. Anti aldehyde **6** delivered highly diastereoselective reactions with lithium and 9-BBN methyl ketone enolates with a 1,2-anti relationship in aldol adduct **7**. Syn aldehyde **8** did not show this same highly selective formation for aldol adduct **9**. However since the ketone enolate we intended to employ was also chiral, both syn and anti aldehydes would be investigated. In addition, only 9-BBN boron enolates are employed in the Cee and Siska work. Given the boron ligand effect discovered by Dr. Welch (Tables 1.2 and 1.3), a more thorough investigation of boron reagents was in order.

**Table 2.1** Cee and Siska precedent.[4]




| | 1,2-*anti* : 1,2-*syn* (% yield) | | |
|---|---|---|---|
| | M = $TMS/BF_3{\cdot}OEt_2$ | M = 9-BBN | M = Li |
| R | $CH_2Cl_2$ | $CH_2Cl_2$ | THF |
| Me | 65 : 35 (83) | 91 : 09 (88) | >99 : 01 (95) |
| *i*-Pr | 41 : 59 (95) | 86 : 14 (92) | >99 : 01 (98) |
| *t*-Bu | 09 : 91 (89) | 81 : 19 (90) | >99 : 01 (98) |




| | 1,2-*anti* : 1,2-*syn* (% yield) | | |
|---|---|---|---|
| | M = $TMS/BF_3{\cdot}OEt_2$ | M = 9-BBN | M = Li |
| R | $CH_2Cl_2$ | $CH_2Cl_2$ | THF |
| Me | 67 : 33 (78) | 45 : 55 (86) | 63 : 37 (95) |
| *i*-Pr | 49 : 51 (67) | 36 : 64 (83) | 84 : 16 (87) |
| *t*-Bu | 18 : 82 (37) | 33 : 67 (86) | 66 : 34 (70) |

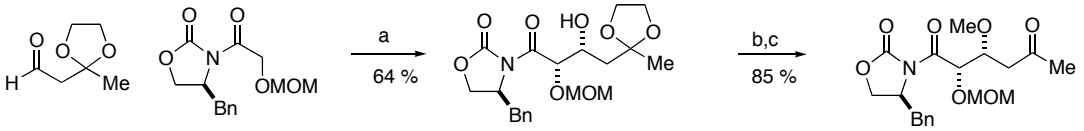
(3) Evans, D. A.; Cee, V. J.; Siska, S. J.; *J. Am. Chem Soc.* **2006**, *128*, 9433- 9441.

(4) This table is reproduced with the permission of Dr. Dennie Welch from his post-doctoral report.

## Synthesis of the $C_1$–$C_6$ Fragment

The synthesis of the $C_1$–$C_6$ fragment **3** was straightforward. Compound **3** was prepared according to the procedures developed by Dr. Welch (scheme 1.27)[5], and hydrolysis of the acetal produced **3**, which was used for the subsequent fragment coupling studies.

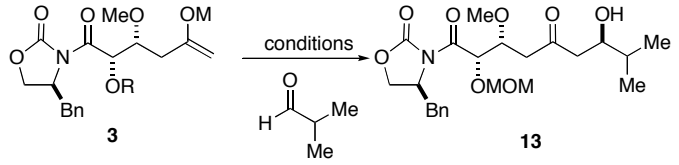
**Scheme 2.1**




a), $Bu_2BOTf$, *i*-$Pr_2NEt$., then **11**, $CH_2Cl_2$ -70 °C; b) $Me_3OBF_4$, proton sponge, $CH_2Cl_2$; c) PPTS, acetone, Δ.

The intrinsic diastereoselectivity of aldol reactions of this methyl ketone with isobutyraldehyde to give aldol adduct **13** were also explored. In light of Dr. Welch's results showing that the ligands on boron could have an effect on the diastereoselectivity of the $C_6$–$C_7$ bond construction, enolizations using 9-BBNOTf, $Bu_2BOTf$, $PhBCl_2$ and $Cy_2BCl$ were all attempted (Table 2.2). Use of $Bu_2BOTf$ and $PhBCl_2$ led to decomposition of ketone **3**. Enolizations with 9-BBNOTf and $Cy_2BCl$ both gave modest diastereoselectivity favoring the desired product. The diastereoselectivity is lower than what is typically observed in 1,5-anti aldol reactions, but consistent with that observed with Paterson in similar experiments on his $C_1$–$C_6$ peloruside fragment (Equation 1.2) and those by Dr. Welch (Table 1.1).

**Table 2.2** Studies of intrinsic bias of **3**.




| entry | M | solvent | dr |
|---|---|---|---|
| 1 | $Bu_2B$ | toluene | decomposition |
| 2 | $Cy_2B$ | toluene | 1.9 : 1 |
| 3 | PhBCl | toluene | decomposition |
| 4 | 9-BBN | toluene | 4.0 : 1 |

(5) In this sequence I began by using the $C_2$ benzyloxy analogue of **12** prepared by Mr. Stephen Ho, an undergraduate in our lab, and also prepared compounds **10** and **12** myself. Compound **11** was prepared by Mr. Stephen Ho. The $C_2$ benzyloxy compound may be converted to **3** by the following sequence: methylation of the $C_3$ alcohol, $C_2$ benzyloxy hydrogenolysis, $C_2$ MOM protection, and $C_5$ ketal hydrolysis. The overall yield for this sequence was inferior to the sequence shown.

Entry 1 was repeated twice, to ensure that the observed decomposition of **3** was not a fluke. Since $Bu_2BOTf$ caused decomposition, its use was not investigated any further in the $C_6$–$C_7$ bond construction studies. The most important result from this table, was that 9-BBNOTf, the most effective reagent in the Cee and Siska studies for addition into anti-α,β oxygenated aldehydes bearing our protecting group strategy, was compatible with a MOM group at the $C_2$ alcohol.[6]

Concurrently, Dr. Welch had prepared aldehydes **4**, **14** and **15** (Figure 2.2). Their preparation will not be discussed in detail as it bears close resemblance to fragments employed by Dr. Reichelt (see scheme 1.22) and this protecting group strategy was ultimately superseded as will be shown shortly.

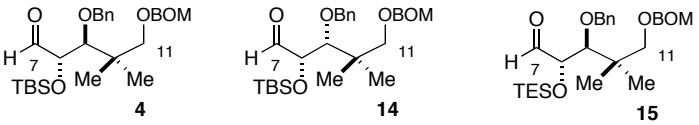
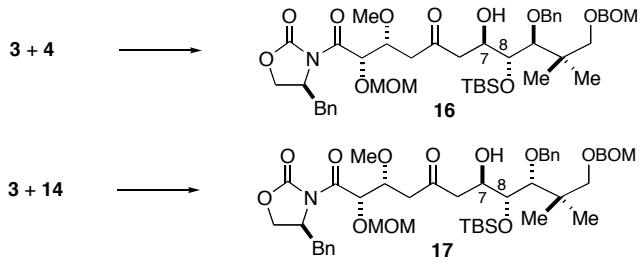



**Figure 2.2** Aldehydes prepared by Dr. Welch

I conducted preliminary fragment coupling investigations, which showed that a 9-BBN triflate mediated aldol reaction with anti aldehyde **4** would be effective for the bond construction producing aldol adduct **16**. Conditions could not be found to produce aldol adduct **17** from syn- aldehyde **14** in high diastereoselectivity.

**Table 2.3** Preliminary investigation of the $C_6$-$C_7$ bond construction



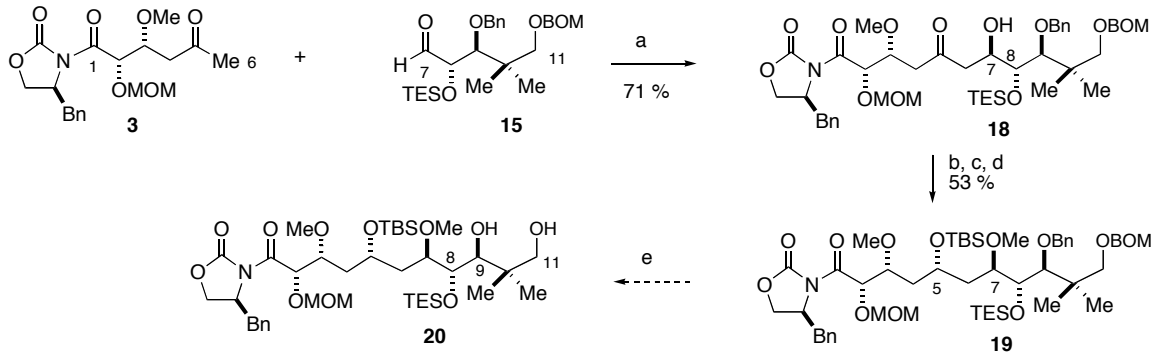

| entry | M | solvent | 7,8 anti: 7,8 syn |
|---|---|---|---|
| 1 | 9-BBN | toluene | > 20:1 |
| 2 | $Cy_2B$ | toluene | 1: 2.5 |

| entry | M | solvent | 7,8 anti: 7,8 syn |
|---|---|---|---|
| 1 | 9-BBN | toluene | 1: 2.4 |
| 2 | $Cy_2B$ | toluene | 1: 1.4 |

(6) Recall Dr. Welch's finding that 9-BBNOTf was ineffective at effecting an aldol reaction on a $C_2$ OTBS protected version of 4 (Table 1.1).

Dr. Welch wished to improve the yield of the global deprotection, and he felt that the $C_8$ alcohol was one of the most crowded in the molecule. Accordingly he prepared aldehyde **15** with the anticipation that a TES group protecting the $C_8$ alcohol would ultimately increase the ease of global deprotection. I conducted a preparative scale fragment coupling on this compound (Scheme 2.2). Interestingly the diastereoselectivity in aldol adduct **18** fell to 10:1, which must be related to the smaller size of the TES protecting group.

**Scheme 2.2**




a) **3**, 9-BBNOTf, $Et_3N$, toluene, then **15**, -78 °C; b) $Me_4N$ $HB(OAc)_3$, AcOH, $CH_3CN$, -30 °C, c) TBSCl, im, DMF; d) $Me_3OBF_4$, proton sponge®, e)$Pd(OH)_2/C$, $H_2$, $CH_3CN$.

Dr. Welch carried the material I had prepared forward to elaborated fragment coupling product **19**, and unfortunately found that the TES group at the $C_8$ alcohol was labile towards the hydrogenolysis employed to remove the benzyl and BOM groups at $C_9$ and $C_{11}$ in the preparation of **20**.[7] Accordingly Dr. Welch designed $C_7$–$C_{11}$ fragment **22** with TBS protection at $C_8$, shown in figure 2.3. It was also decided to exploit the lability of a TES group to hydrogolysis conditions and use this protecting group on $C_{11}$. This avoided difficult separations early in the synthesis associated with byproducts of BOM chloride.

(7) The lability of TES to hydrogenolysis has been reported: (a) Kim, S.; Jacobo, S. M.; Chang, C.-T.; Bellone, S.; Powell, W. S.; Rokach, J. *Tetrahedron Lett.* **2004**, *45*, 1973- 1976. (b) Rotulo- Sims, D.; Prunet, J. *Org. Lett.* **2002**, *4*, 4701- 4704.

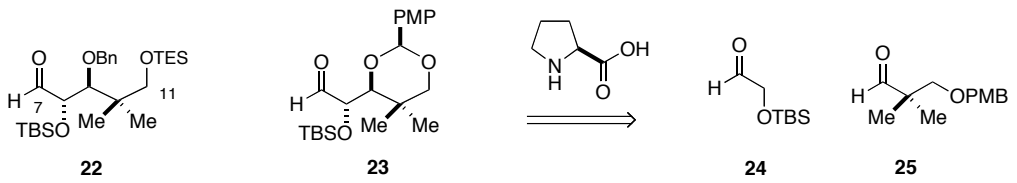



**Figure 2.3** Redesigned $C_7$–$C_{11}$ fragments

I hypothesized that an alternate $C_7$–$C_{11}$ fragment, **23**, could be prepared by a crossed organocatalytic aldol of aldehyde **24** and aldehyde **25** followed PMB oxidation.[8] The oxidatively formed PMP acetal would serve as a common protecting group on $C_9$ and $C_{11}$. Unfortunately aldehyde **25**, prepared in 2 steps from neopentyl glycol proved to be unreactive in the crossed aldol, which may be attributed to steric hindrance.

Dr. Welch encountered some difficulty in the synthesis of the redesigned $C_7$–$C_{11}$ fragment, so I joined him to assist on this task.

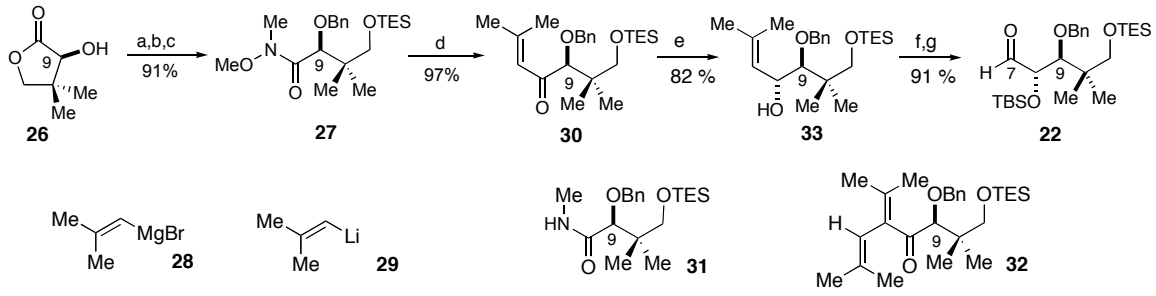
**Synthesis of the Anti $C_7$–$C_{11}$ Fragment**

*(S)*-Pantolactone **26** was converted into Weinreb amide **27** in 3 steps by Dr. Dennie Welch and Mr. Stephen Ho (Scheme 2.3). Dr. Welch discovered that addition of Grignard reagent **28** to this Weinreb amide resulted in decomposition related to TES group cleavage. This decomposition was attributed to the Lewis acidic nature of the magnesium salts. On small scale, the addition of vinyllithium **29** was found by Dr. Welch to be a viable route to enone **30**. Scaling of this reaction proved to be difficult. Dr. Welch found that the lithium halogen exchange reaction was very slow, and premature addition of the enone resulted in products that did not arise from vinyllithium addition. I ultimately developed a procedure that could be run on gram scale with high yield. The method of preparation of the vinyllithium was crucial to the success of the reaction. The lithium halogen exchange was conducted at 0 °C, and aged for an hour before addition of the enone. Failure to perform this aging process or running the lithium halogen exchange at lower temperatures led to recovery of an amide containing product **31** where the OMe

(8) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 6798-6799.

group was absent.[9] Conversely, if the temperature of the lithium halogen exchange was allowed to rise to more than 15 °C over the course of the addition of the vinyl bromide, an enone containing product **32**, incorporating a diene derived from two of the vinyl moieties was detected, presumably through the intermediacy of vinylidene carbenes.[10] The aging process presumably involves destruction of *t*-butyllithium by reaction with diethyl ether. Such a process creates ethylene, which can react with *t*-butyllithium to produce neohexyllithium. Fortunately, no products arising from neohexyllithium addition to the Weinreb amide were observed. It should be noted Dr. Welch also developed a procedure that involved a longer warming at a lower temperature with MTBE as solvent, and this gave a similar result, but was not run on a scale greater than 300 mg. Dr. Welch showed that enone **30** could be converted into anti diol **33** and TBS protection and ozonolysis produced aldehyde **22**.

**Scheme 2.3**




a), $BnON(H)CCl_3$,TfOH, hexanes/ $CH_2Cl_2$; b) $Me_3Al$, MeON(H)Me·HCl, $CH_2Cl_2$, 0 °C; c)TESCl,$Et_3N$, DMAP, $CH_2Cl_2$ ; d) $(CH_3)CHBr$, *t*-BuLi, $Et_2O$, see text. e) $Zn(BH_4)_2$, $Et_2O$, –30 °C; f), TBSCl, $Et_3N$, DMAP, DMF g), $O_3$, then $PPh_3$, $CH_2Cl_2$

I conducted the scale-up of these reactions, and the procedures and yields reported in the supporting information were from my work.

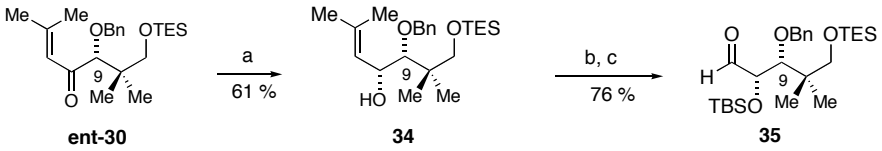
(9) Beak, P.; Selling, G. W. *J. Org. Chem.* **1989**, *54*, 5574-5580.

(10) The structure of the diene containing product and the Des-OMe Weinreb amide were elucidated by Dr Welch.

## Synthesis of the Syn $C_7$–$C_{11}$ Fragment

To conduct a more thorough investigation into the key fragment coupling, a fragment epimeric with **22** at $C_9$ was prepared.[11] I prepared this fragment from **ent-30** via a reduction using DiBAlH to give allylic alcohol **34**. Subsequent protection and ozonolysis afforded fragment **35** (Scheme 2.4**)**. Dr. Welch had used this method to prepare fragment **14** in the old protecting group scheme.

**Scheme 2.4**



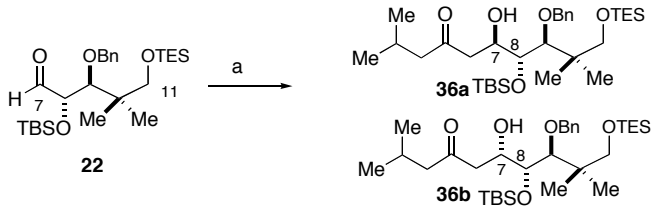

**ent-30** **34** **35**

a) DiBAlH, $CH_2Cl_2$, -78 °C b) TBSCl, $Et_3N$, DMAP, DMF c) $O_3$, then $PPh_3$, $CH_2Cl_2$ -78 °C

## Investigation of the $C_6$–$C_7$ Bond Construction with the Anti $C_7$–$C_{11}$ Fragment

The results described in Scheme 2.2 and Table 2.3 led us to be optimistic about the success of the projected fragment coupling with methyl ketone **3**. However, for the purposes of being thorough, the intrinsic facial preferences of fragment **22** were studied using methyl isobutyl ketone (MIBK) as an achiral enolate, leading to aldol adducts **36** (Table 2.4).

**Table 2.4** Investigation of the intrinsic diastereoselectivity of **22**.




**22**

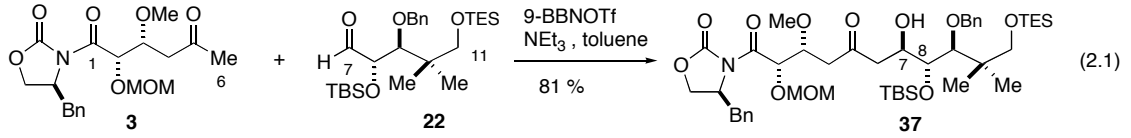
| entry | M | solvent | 36a: 36b |
|---|---|---|---|
| 1 | 9-BBNOTf | toluene | no reaction |
| 2 | $Cy_2BCl$ | toluene | 1: 3 |
| 3 | $Bu_2BOTf$ | toluene | 1: 1 |

a) methyl isobutyl ketone, M, $NEt_3$, then **22**, -78 °C

Surprisingly, the 9-BBN enolate of MIBK did not react under these conditions. The $Cy_2B$ enolate gave primarily the undesired stereochemistry at $C_7$, while the $Bu_2B$ enolate

(11) There is a significant price difference between (*S*)- Pantolactone **26** ($133 for 1 g, 7.7 mmol, only size available from Aldrich, April 22nd 2012) and (*R*)-Pantolactone ($52 for 25g, 192 mmol, largest size available from Aldrich, April 22nd, 2012). Since the synthesis of **22** uses the more expensive enantiomer, this may have implications for the synthesis of sufficient quantities of peloruside A to conduct pharmaceutical trials. An approach to peloruside A using the less expensive **35** bears investigating.

gave no selectivity. Fortunately despite the results of table **2.4**, the desired fragment coupling worked very well to afford aldol adduct **37** (equation 2.1).




(2.1)

The diastereoselectivity in this reaction is over 30:1, which is greater than the 20:1 diastereoselectivity obtained with BOM at $C_{11}$ (Table 2.3, entry 1) It is unclear if this is a remote gearing effect, or if the diastereoselectivity increases with increased reaction scale. It is also unclear why 9-BBN triflate works so well in this reaction, but does not mediate a reaction with MIBK. Since 9-BBN enolates of simple methyl ketones work well in the Cee and Siska work (Table 2.1) we presume that the $C_{10}$ geminal dimethyl group reduces the reactivity of **22**. The 9-BBN enolate of **3** must be more reactive than the 9-BBN enolate of MIBK. It was noted that the enolates of **3** formed with 9-BBN triflate are deep red- violet in colour, while the 9-BBN enolate of MIBK was relatively colourless. This colour could indicate some sort of charge transfer complex, which may increase the reactivity of the enolate. An interesting future line of work would be conducting EPR measurements on 9-BBN enolates, or allowing them to react in reactions that may involve the intermediacy of radicals.[12]

The reasons for the ligand effects observed on boron throughout this work are also unclear. A minimization of dipoles leading to a Cornforth transition state model **38** in the Cee and Siska work was proposed to account for the high diastereoselectivity of additions into anti α,β-oxygenated aldehydes (Figure 2.4).[3] For the fragment coupling between **3** and **22**, this may be merged with the Goodman model for 1,5-anti aldol induction

(12) Enolates of metals that are arguably $d^0$, such as Ti(IV) are known have radical character. See: Beaumont, S.; Ilardi, E. A.; Monroe, L. R.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 1482-1483. And references therein. Boron centered radicals are also known: Walton, J. C.; Brahmi, M. M.; Monot, J.; Fensterbank, L.; Malacria, M.; Curran, D. P., Lacôte, E. *J. Am. Chem. Soc*. **2011**, *133*, 10312- 10321.

involving a formyl hydrogen bond and boat- like closed transition state, shown in model **39**. [13]

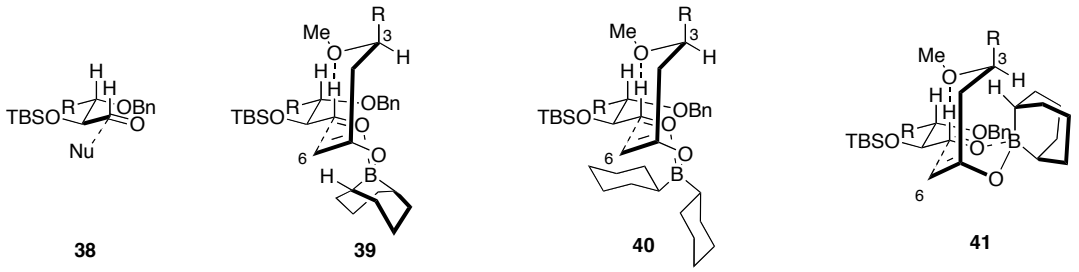



**Figure 2.4** Possible transition states for the $C_6$–$C_7$ bond construction.

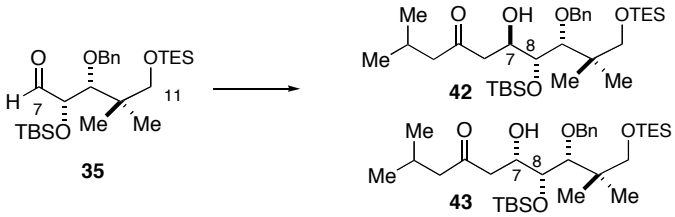
From inspection of model **39**, it appears the 9-BBN ligand on the boron does not significantly interact with anything else. The substituents on the ligand are in effect "tied back". The larger cyclohexyl ligands shown in **40** would interact with $C_6$ of the methyl ketone. In a non-boat transition state, shown in **41**, the ligands on the boron interact with $C_3$. Unfortunately this does not explain the ligand effect observed in table **2.4**, since MIBK does not contain oxygenation β' to the ketone, yet shows a ligand effect in the aldol reactions. An alternate explanation that does not rely on the Goodman model may be that bulky boron species such as dicyclohexylboryl do not undergo reactions via closed transition states with α,β-oxygenated aldehydes. In the Cee and Siska work, Mukaiyama aldol reactions were unselective with anti α-silyloxy, β-benzyloxy aldehydes (Table 2.1 M= TMS/$BF_3$•$Et_2O$).

### Investigation of the $C_6$–$C_7$ Bond Construction With the Syn $C_7$–$C_{11}$ Fragment

The aldol reactions with syn aldehyde **35** were also studied. The initial experiments examined ligand effects on the intrinsic stereochemistry. The results are summarized in table 2.5.

(13) Paton, R. S.; Goodman, J. M.; *J. Org. Chem.* **2008**, *73*, 1253- 1263.

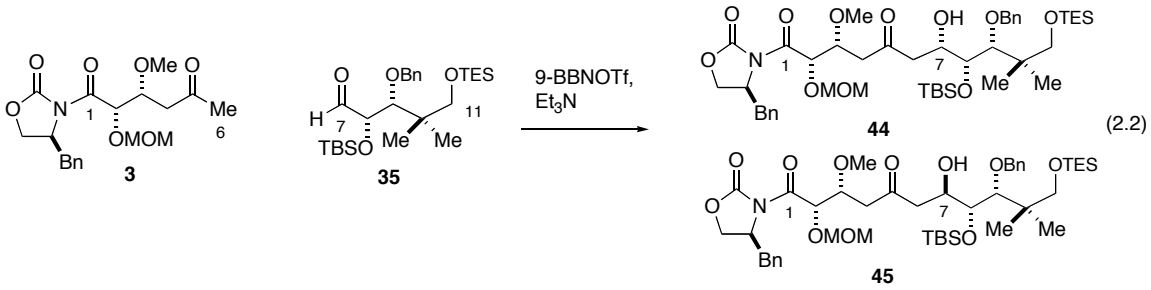
**Table 2.5** Intrinsic diastereoselectivity of **35**.



| entry | M | solvent | 42: 43 |
|---|---|---|---|
| 1 | 9-BBNOTf | toluene | 1: 9 |
| 2 | $Cy_2BCl$ | toluene | 1: 1.4 |

a) methyl isobutyl ketone, M, $NEt_3$, then **35**, -78 °C

In this case, a reaction did proceed under both conditions to give aldol adducts **42** and **43**. In neither case was there selectivity for the desired product. The d.r. observed for 9-BBNOTf was higher than any observed in the Cee and Siska cases for syn α,β-oxygenated aldehydes. This bias for the incorrect stereochemistry at $C_7$ is in line with the results obtained for aldehyde **14** in table 2.3. The aldol reaction between **3** and **35** was done and found to have a 2:1 preference for undesired $C_7$ stereochemistry **44** to desired $C_7$ stereochemistry **45** (equation 2.2).



(2.2)

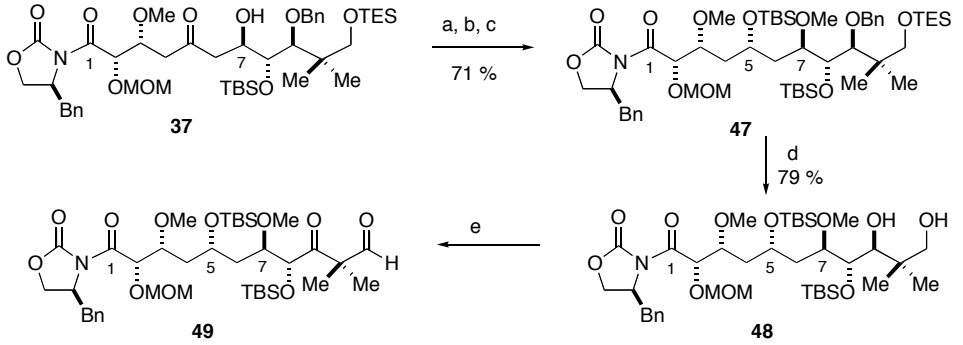
**Elaboration to the β-Keto Aldehyde**

Aldol adduct **37** was elaborated by Dr. Welch in preparation for the next fragment coupling. A 1,3-anti reduction of the $C_5$ ketone proceeded in >10:1 selectivity when $[Me_4N][HB(OAc)_3]$ was used as the reductant.[14] The sodium salt gave inferior diastereoselectivity. Selective TBS protection followed by methylation gave the fully protected $C_1$–$C_{11}$ fragment **47**. Exposure to hydrogenolysis conditions permitted the cleavage of both the benzyl group protecting the $C_9$ alcohol and the TES group protecting the $C_{11}$ alcohol leading to diol **48**. Finally, a Dess–Martin periodinane mediated oxidation

(14) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

delivered β-keto aldehyde **49**. In the course of scale-up, it was found that telescoping the reduction, silylation and methylation steps resulted in slightly higher yield. Ultimately Dr. Welch and I prepared over 2 g of aldehyde **49**.

**Scheme 2.5**

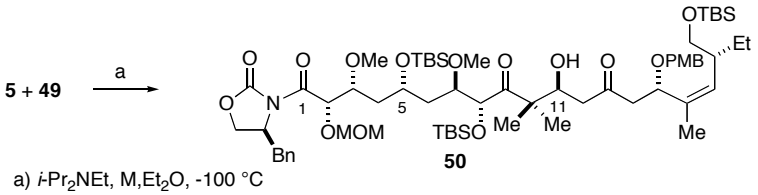



a) $Me_4N\ HB(OAc)_3$, AcOH, $CH_3CN$, -30 °C; b) TBSCl, $Et_3N$, DMF; c)$Me_3OBF_4$, Proton Sponge®, $CH_2Cl_2$; d) $Pd(OH)_2/C$, EtOAc, $H_2$; e) DMP, py, $CH_2Cl_2$

## The $C_{11}$–$C_{12}$ Bond Construction

Dr. Welch had prepared a large quantity of $C_{12}$–$C_{19}$ fragment **5**, and he subsequently investigated the $C_{11}$–$C_{12}$ bond construction. An initial aldol reaction attempt was made using $Cy_2BCl$ on a 0.01 mmol scale. This reaction gave a 2.8:1 mixture of diastereomers in the desired direction with a combined yield of 56%. With this modest yield and selectivity, attention turned to using a $Bu_2BOTf$ aldol reaction (Table 2.6).

**Table 2.6** The $C_{11}$-$C_{12}$ Bond Construction




a) *i*-$Pr_2NEt$, M,$Et_2O$, -100 °C

| entry | M | yield | dr |
|---|---|---|---|
| 1 | $Cy_2BCl$ | 56 % | 2.1 :1 |
| 2 | $Bu_2BOTf$ | 79%- 0% | 12 : 1 |
| 3 | 9-BBNOTf | 92 % | 20: 1 |

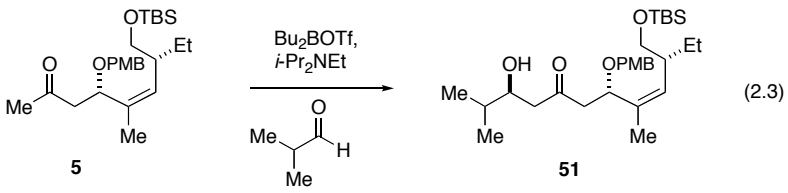
This 1,5-anti aldol reaction proceeded in high yield and diastereoselectivity (79% yield, 12:1 dr) in two attempts, on scales of 0.04 and 0.170 mmol (table **2.6**) to afford peloruside backbone **50**. It was remarkable that the reaction was over in 15 minutes at an internal temperature of -100 °C. We surmise that the electron withdrawing nature of the β-keto substituent and the low steric profile of the $sp^2$ centre combine to increase the electrophilicity of aldehyde **49**. In the course of Dr. Welch's studies, I prepared more

aldehyde **49**, and also successfully ran the reaction twice for myself using Dr. Welch's conditions. In the first attempt, on 0.127 mmol of **49**, the reaction did not work the first time I ran the reaction, but the starting materials were recovered and did react in the second attempt. In the second successful reaction the reaction was run without incident on 0.196 mmol of **49**.

Perplexingly, after my two successful runs of this reaction, I could no longer repeat it, despite subsequent batches of aldehyde **49** having the same analytical properties, even when run on a similar scale under the same conditions.[15] Five failed attempts on scales from 0.090 to 0.429 mmol of **49** were made in total. Attempts to run the reaction at higher temperatures also yielded only trace amounts of product. Aldehyde **49** could be recovered if an oxidative work-up was not employed, but was destroyed if an oxidative work-up was employed. Ketone **5** could always be recovered. All reagents and solvents were repurified, and different batches of $Bu_2BOTf$ were screened but I was not able to identify what variable had permitted the previously successful reaction.[16] I was able to successfully run an aldol reaction between isobutyraldehyde, ketone **5** and $Bu_2BOTf$ from the same batches that failed in the main bond coupling (equation 2.3) to produce aldol adduct **51** in high yield and diastereoselectivity. This experiment showed that the $Bu_2BOTf$ had not gone bad.

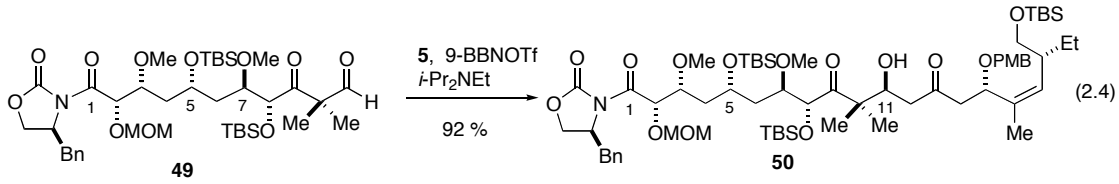
(15) Dr. Welch left the lab after my first successful repetition of the reaction using $Bu_2BOTf$ and before the second time I ran it successfully using $Bu_2BOTf$. Since the problem arose after he left, he could not help me troubleshoot the reaction in person. Through e-mail correspondence, neither of us could locate a variable reliant on our experimental technique. This problem is mentioned in the thesis since it may bear investigating if this route is ever used for future analogue synthesis or preparation of bulk quantities of Peloruside A.

(16) Had the reaction with $Bu_2BOTf$ not initially worked for Dr. Welch, he would have undoubtedly tried 9-BBNOTf next, hence this unknown variable would not have jeopardized the completion of the molecule. In retrospect it unfortunate that $Bu_2BOTf$ worked on the first attempt. While an initial failure at the $C_{11}$-$C_{12}$ bond construction would have been discouraging, using 9-BBNOTf from the start would have saved several hundred milligrams of **49** from destruction during failed scale-up attempts.



(2.3)

As 9-BBNOTf had been so fruitful in prior aldol reactions, I investigated it in the $C_{11}$–$C_{12}$ bond construction. Fortunately this reaction worked, in a higher yield and diastereoselectivity than the successful $Bu_2BOTf$ cases. The aldol reaction mediated with 9-BBNOTf[17] was a robust reaction. It was conducted successfully 7 times out of 7 tries on scales ranging from 0.070 to 0.534 mmol of **49**. The last reaction was the highest yielding, at 92%, giving 600 mg of the peloruside A carbon backbone in a single reaction (equation 2.4).

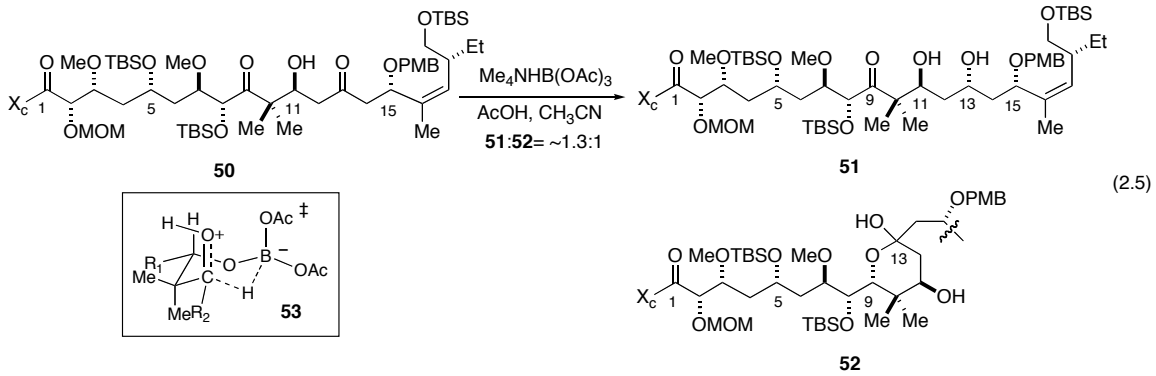


(2.4)

## II. The $C_9$- $C_{13}$ Ketone Selectivity Problem

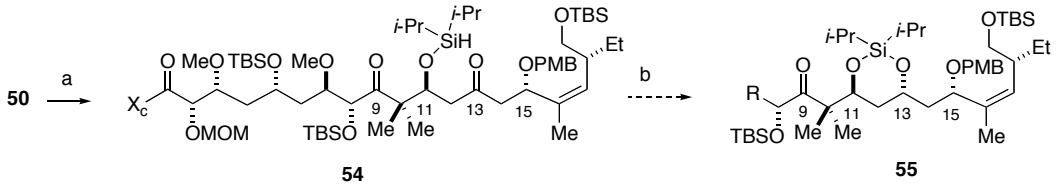
After Dr. Welch obtained aldol adduct **50**, he attempted to conduct a 1,3-anti reduction to relay the stereochemistry from $C_{11}$ to $C_{13}$ to give $C_{11}$–$C_{13}$ diol **51**. Unfortunately, little site selectivity for the $C_{13}$ ketone was observed, with competitive reduction of the $C_9$ ketone occurring (equation 2.5). The products were readily separable as the reduction of the $C_9$ ketone led to the formation of hemiacetal **52**.

(17) Two different batches of 9-BBNOTf were used, one prepared by Dr. Welch and freshly distilled, and one prepared by Dr. Jason Burch in 2004 and not repurified since its initial purification. Both gave similar results. The Burch 9-BBN triflate was used in the highest yielding reaction.




Dr. Welch attempted to optimize this reaction by changing the solvent composition to run the reaction at a lower temperature, but no improvement was noted. We had not initially predicted that this transformation would be problematic since we felt that the geminal dimethyl group at $C_{10}$ would prevent reduction of the $C_9$ ketone. In retrospect, since this transformation goes through a chair-like transition state **53**, the geminal methyl groups are as far as possible from the ligands on the boron, so the lack of a steric effect is understandable. A final attempt was made to do an intramolecular hydrosilylation as reported by Davis.[18] Accordingly aldol adduct **50** was silylated with chlorodiisopropylsilane to give silyl hydride **54** and exposed to $MgCl_2$. Unfortunately this resulted in decomposition and no formation of silyl acetal **55** (Scheme 2.6).[19]

Scheme **2.6**



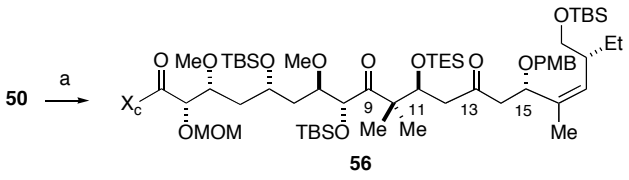

At this point, Dr. Welch's post-doctoral stay in the Evans group came to an end, and I took over primary responsibility for the project.

(18) Anwar, S.; Davis, A. P. *Tetrahedron*. **1988**, *44*, 3761-3770.

(19) Dr. Welch felt that $MgCl_2$ was the mildest Lewis acid among those reported by Davis in his substrate table. We had a great deal of trepidation about the prospects of the proposed transformation since there are so many Lewis basic ethers and carbonyls on **54**. Because of this trepidation, I made the decision to abandon this approach prematurely. The successful implementation of this approach may be found in section **III** of this Chapter.

I initially attempted several other reductions to reduce $C_{13}$ (Table 2.7). $SmI_2$ in methanol resulted in decomposition of **50**.[20] An attempt to effect a PMB directed 1,3-syn reduction with $Zn(BH_4)_2$ in $Et_2O/CH_2Cl_2$ also failed. The free alcohol on **50** was masked with a TES group to give TES protected aldol adduct **56**. Selectivity for reduction of the $C_{13}$ over $C_9$ ketone could be achieved on **56** with CBS catalyst and borane THF, but no facial selectivity was observed giving diastereomeric compounds **57**.[21] Finally, the $Zn(BH_4)_2$ reduction was re-attempted on **56**, but in this case the substrate failed to react

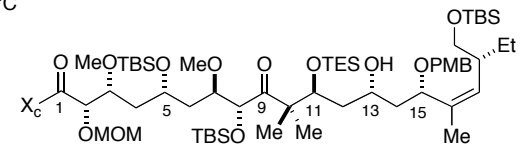
**Table 2.7** Attempts at $C_{13}$ ketone reduction.



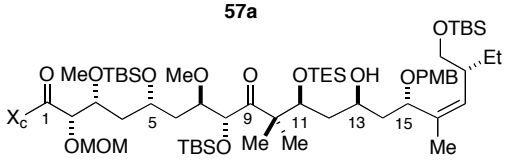

**56**

a) TESOTf, 2,6 Lutidine, $CH_2Cl_2$ -78 °C

| entry | Substrate | Conditions | Result |
|---|---|---|---|
| 1 | **50** | $Zn(BH_4)_2$ | decomposition |
| 2 | **50** | $SmI_2$ | decomposition |
| 3 | **56** | (*R*)-CBS | 1: 1 **57a** : **57b** |
| 4 | **56** | $Zn(BH_4)_2$ | no reaction |




**57a**




**57b**

### Attempt to Construct the $C_{11}$–$C_{12}$ Bond with $C_9$ at the Alcohol Oxidation State

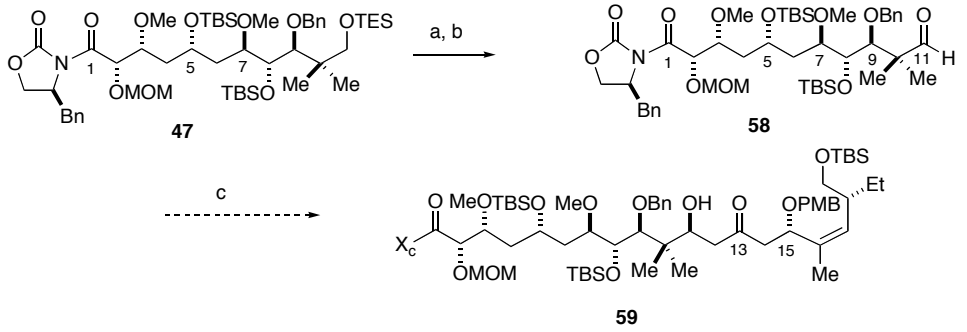
With these discouraging results, the decision was made to sacrifice some of the convergency of the synthesis, and attempt the $C_{11}$–$C_{12}$ bond construction with $C_9$ still in the alcohol oxidation state. It was unclear if the buried benzyl group could be removed by hydrogenolysis in the presence of the $C_{16}$–$C_{17}$ olefin, but a study to prove the principle could be tested before any protecting group modifications needed to be made.

(20) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172-2173.

(21) The choice of (*R*)-CBS catalyst was arbitrary. The enantiomeric catalyst was not tried. It was not obvious from inspection of the substrate that $C_{13}$ on **56** had a large and small substituent, which was probably confirmed by the absence of diastereoselectivity in the reduction.

Accordingly the TES group of compound **47** was deprotected and oxidized to yield aldehyde **58**. Aldol reactions were attempted with ketone **5** using 9-BBNOTf, $Bu_2BOTf$ and $Cy_2BCl$. In none of these cases was any aldol adduct **59** isolated (Scheme 2.7).

**Scheme 2.7**



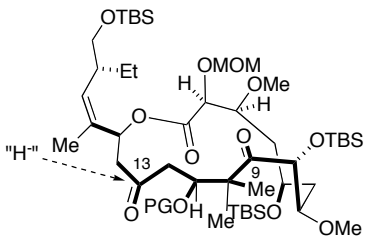

a) CSA, MeOH/ $CH_2Cl_2$, 0°C; b) DMP, py, $CH_2Cl_2$, 0°C; c) M, *i*-$Pr_2NEt$ or $Et_3N$, $Et_2O$, -78 °C to 0 °C

At the time, the lack of reactivity was attributed to the increased steric hindrance at $C_9$. It is surprising in light of the analogous bond construction reported by Hoye.[22] The boron aldol reaction attempts shown in scheme 2.7 were repeated several times, and so the conclusion this substrate was not reactive is judged to be reliable. Since Dr. Welch, Dr Reichelt and I have all conducted $C_{11}$–$C_{12}$ aldol bond constructions on systems that are truncated at $C_6$ (for example see reaction c in Scheme 1.25), it seems reasonable to surmise that the failure of **58** to react is an example of long range gearing effect.

**Studies on $C_{13}$ Keto Seco Acids**

Since the ketone at $C_9$ appeared to be necessary for the $C_{11}$–$C_{12}$ bond construction with our current protecting group scheme, and since no viable method appeared to exist to selectively reduce the $C_{13}$ ketone in the presence of the $C_9$ ketone on a linear substrate, the idea of conducting a macrocyclization with both the $C_{13}$ and $C_9$ ketones in place, followed by a selective reduction of the $C_{13}$ ketone was considered. Such a reduction would now take place on a macrocycle such as **60**, opening the possibility that one face of the ketone would be shielded by pointing inside the macrocycle (Figure 2.5**)**.

(22) See Scheme **1.12** in Chapter **1**.




**60**

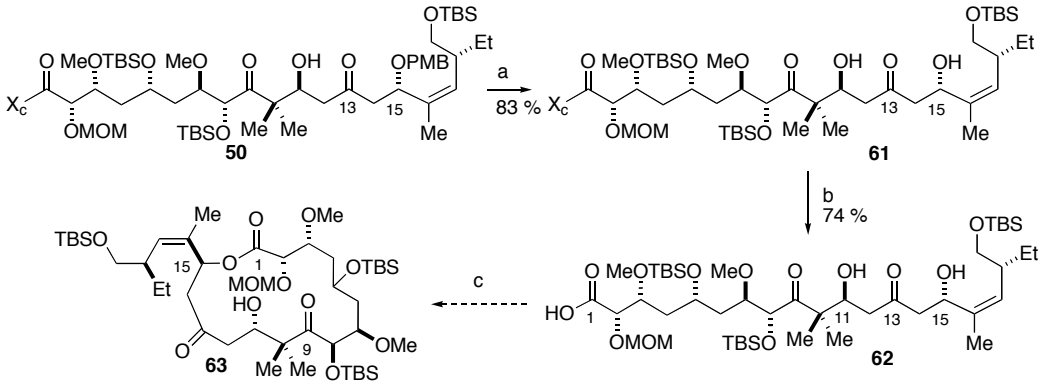
**Figure 2.5** Imagined peripheral attack selective for $C_{13}$ ketone.

A peripheral attack could lead to high facial selectivity, but the sense of this selectivity was not immediately obvious.[23] Higher selectivity for the $C_{13}$ ketone over the $C_9$ ketone was anticipated for an intermolecular hydride delivery, since the $C_{10}$ geminal dimethyl group would potentially be in a position to interact with an oncoming nucleophile in a Bürgi-Dunitz trajectory. This scheme could be implemented quickly from the materials available, and was tested.

**Synthesis of the $C_{11}$ OH Seco Acid**

Aldol adduct **50** was subject to DDQ to remove the $C_{15}$ alcohol PMB protecting group, yielding diol **61**, followed by lithium hydroperoxide cleavage of the oxazolidinone at $C_1$ to yield seco acid **62** (Scheme 2.8).[24]

**Scheme 2.8**




a) DDQ, pH 7 Buffer, $CH_2Cl_2$; b) LiOH, $H_2O_2$, THF c) 2,4,6 trichlorobenzoyl chloride, *i*-$Pr_2NEt$, then DMAP, toluene or 2,6 MNBA, DMAP, $CH_2Cl_2$

(23) Still, W. C.; Galynker, I. *Tetrahedron*. **1981**, *37*, 3981-3996.

(24) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron. Lett.* **1987**, *28*, 6141-6144.

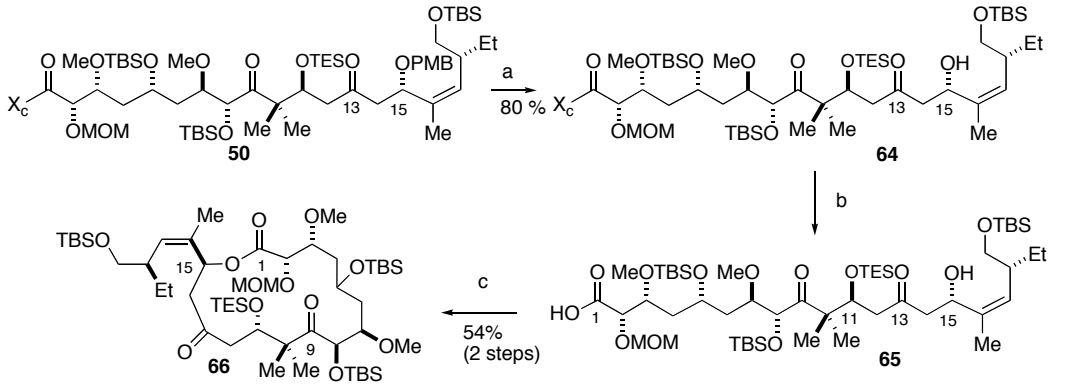
Macrolactonization under either Shiina or Yamaguchi conditions gave very messy mixtures. Mass spectral analysis showed minor peaks corresponding to the mass of macrolactone **63**, but the major peaks corresponded to that mass minus water.

Dehydration of the $C_{11}$ alcohol by an $E_1CB$ mechanism following macrolactonization was postulated based on an NMR analysis showing extra alkenes, and the presence of an ester attachment on the $C_{15}$ oxygenation (based on a downfield change in the chemical shifts of the $C_{15}$ CH signal). Because of the downfield shift of the $C_{15}$ CH, macrocyclization site selectivity between the $C_{11}$ and $C_{15}$ alcohol was not judged to be a problem.

**Synthesis of the $C_{11}$ TES Seco Acid and Macrolactonization Studies**

After this disappointing setback, it was decided to try the analogous sequence of events with $C_{11}$ TES protected macrolactone in the hopes that this would not undergo an $E_1CB$ elimination (Scheme 2.9). Accordingly $C_{11}$ TES protected aldol adduct **57**, available from the reduction studies in table 2.7 was converted to diol **64** and then to seco acid **65**. Gratifyingly, seco acid **65** could be cyclized under Yamaguchi conditions to gave macrocycle **66**.

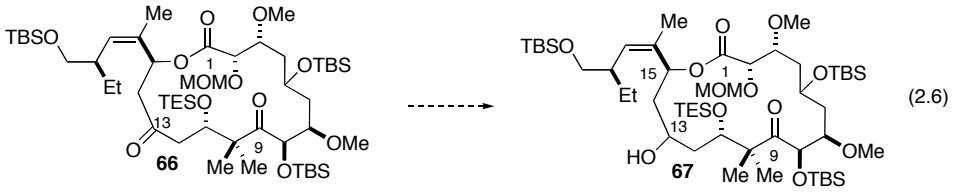
**Scheme 2.9**




a) DDQ, pH 7 Buffer, $CH_2Cl_2$; b) LiOH, $H_2O_2$, THF c) 2,4,6 trichlorobenzoyl chloride, *i*-$Pr_2NEt$, then DMAP, toluene

**Attempts to Reduce the $C_{13}$ Ketone**

With $C_{13}$ keto macrocycle in hand, reduction attempts of the $C_{13}$ ketone were attempted (Equation 2.6).



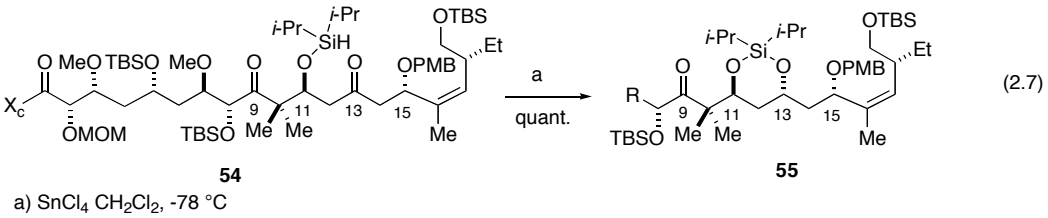

(2.6)

Surprisingly the ketone at $C_{13}$ was amazingly resistant to reduction. Treatment with reductants such as K-Selectride®, L-Selectride®, sodium borohydride, lithium borohydride, tetramethylammonium triacetoxyborohydride and potassium triethylborohydride resulting in either recovery of starting material or decomposition. Nothing with a mass corresponding to **67** was ever isolated. Treatment with multiple equivalents of sodium borohydride in methanol resulted in low yields of a compound with a mass equivalent to a compound with both ketones reduced. It was speculated that the $C_{13}$ ketone was unexpectedly hindered, but upon reduction of the $C_9$ ketone under forcing conditions, a conformational change occurred and the $C_{13}$ ketone was immediately reduced. The $C_{11}$ TES group may provide too much steric hindrance to enable reduction of the $C_{13}$ ketone. Removal of the $C_{11}$ TES group was not attempted since the efforts described in the next discussion became fruitful and so efforts were switched to that strategy.

## III. Completion of the Synthesis

In light of the difficulties encountered in reducing the ketone at $C_{13}$ on macrocycle **66**, attention returned to reducing the ketone at $C_{13}$ on a linear substrate. Inspection of our chemical inventory revealed several mg of silane **54**. The original Davis reference showed that tin tetrachloride gave the highest yield for intramolecular hydride delivery in several substrates, accordingly silane **54** was exposed to 20 mol% tin tetrachloride in dichloromethane for 2 hours at -78 °C. Monitoring by TLC showed no apparent reaction,

and allowing an aliquot to warm to higher temperatures showed extensive decomposition. The reaction was accordingly quenched in anticipation of recovering the substrate to screen other Lewis acids.[25] However, NMR analysis of the recovered material from the reaction revealed that the desired reaction had indeed taken place with exquisite site and diastereoselectivity (equation 2.7).




(2.7)

Our hypothesis for the high site selectivity is that the bulky Lewis acid tin tetrachloride selectively complexes to the less hindered ketone, promoting hydride delivery to that site as shown chair-like transition state **68** (Figure 2.6).

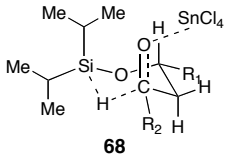



**Figure 2.6** Rationale for site and diastereoselectivity.

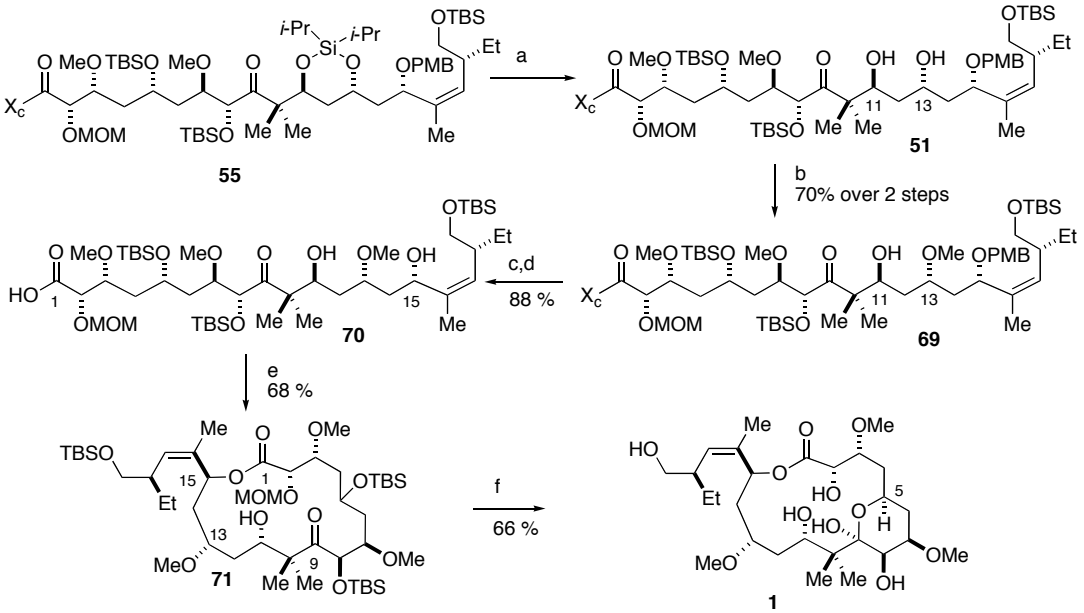
**Elaboration to the Seco Acid and Macrolactonization**

The silyl acetal in **55** proved to be relatively robust, being resistant to both a basic aqueous work-up and chromatography. Brief exposure to acetic acid buffered TBAF resulted in a cleavage of the silyl acetal without competitive deprotection of the other silyl protecting groups in the molecule. The diol so obtained matched diol **51**, prepared by Dr. Dennie Welch. Exposure of diol **51** to a large excess of Meerwein salt allowed selective methylation of the $C_{13}$ alcohol to produce **69**. It should be noted that extended reaction times resulted in the methylation of the $C_{11}$ alcohol as well, so the reaction was

(25) This is a potentially career-changing example of the importance of taking crude NMR spectra.

carefully monitored.[26] Cleavage of the $C_{15}$ PMB group and hydrolysis of the oxazolidinone at $C_1$ yielded the desired seco acid **70** (Scheme 2.10).

**Scheme 2.10**




a) TBAF, AcOH, THF, 0°C; b) $Me_3OBF_4$, Proton Sponge®, $CH_2Cl_2$; c) DDQ, pH 7 buffer, $CH_2Cl_2$ d) LiOH, $H_2O_2$ THF; e) 2,4,6 trichlorobenzoyl chloride, *i*-$Pr_2NEt$, then DMAP, toluene, 60 °C f) 4NHCl, MeOH

The seco acid was subjected to Yamaguchi macrolactonization conditions, and the desired macrolactone **71** was obtained in good yield. The seco acid contains alcohol functionality at both $C_{11}$ and $C_{15}$, so we were gratified to observe only one macrocycle, corresponding to macrolactonization at the $C_{15}$ alcohol only. Deprotection of the macrolactone to yield peloruside A (**1**) required slight optimization. In our initial route, application of the DeBrabander conditions was uneventful, however a low yield was noted when compound **71** was exposed to these conditions. Our previous route had involved cleavage of all of the silyl groups and cyclization to a tetrahydropyran before exposure to 4N HCl. It was hypothesized that exposure of the ketone containing macrocycle to a 1:1 solution of THF and 4N HCl at room temperature may promote decomposition related to the ketone functionality. We found switching the solvent to

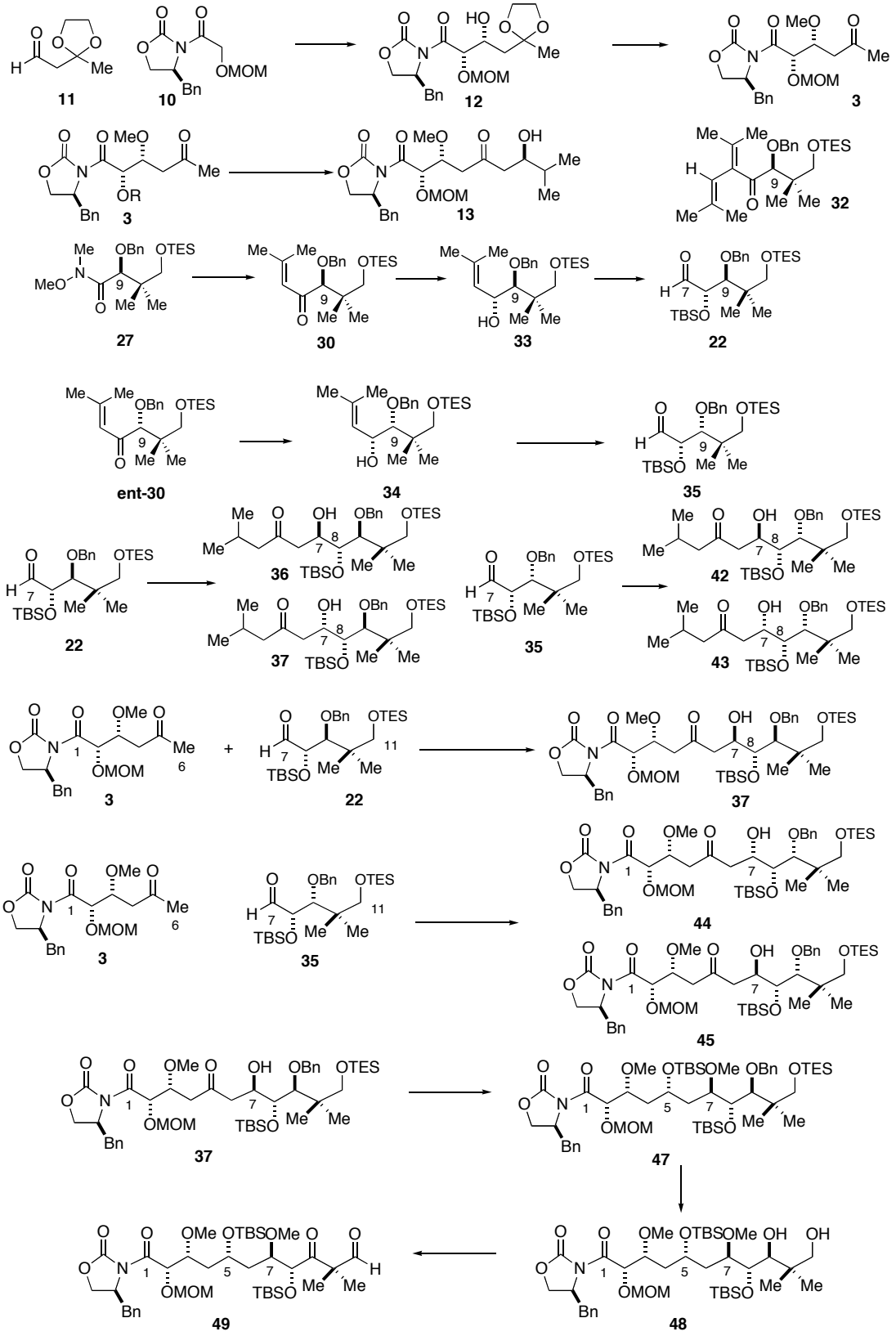
(26) Extended reaction times with fewer equivalents of Meerwein salt led to inferior outcomes. We speculate cyclization of the $C_{13}$ alcohol onto the $C_9$ ketone is competitive.

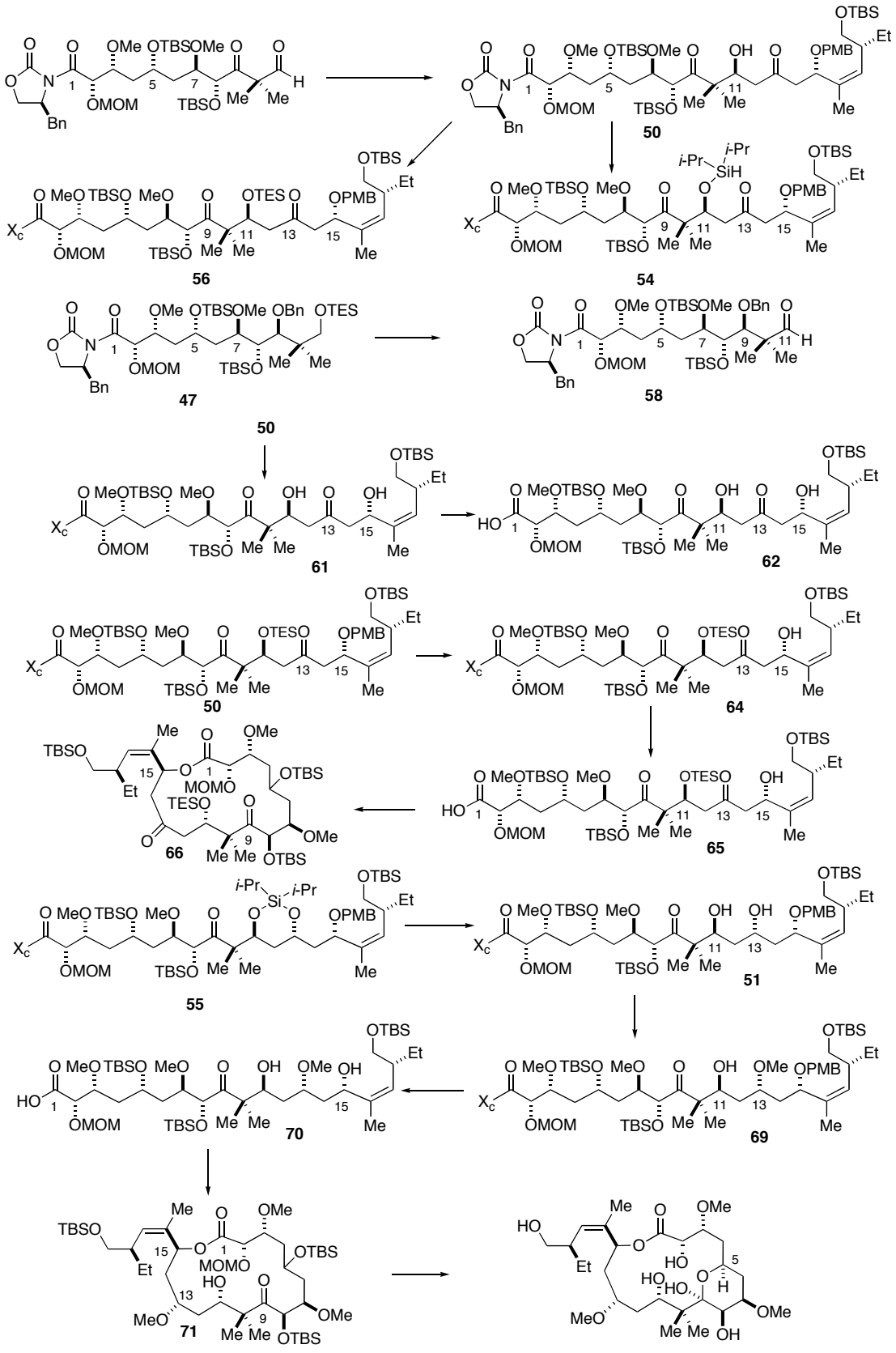
methanol as precedented by Smith improved the cleanliness of the reaction and first running the reaction at 0 °C then warming to ambient temperature further increases the yield. We hypothesize that removal of the silyl protecting groups and concomitant formation of the tetrahydropyran occurs under the milder conditions, and subsequent MOM removal at ambient temperature is now taking place in the absence of the potentially labile keto functionality.

**Conclusion**

A 23 step synthesis of peloruside A was completed. The synthesis was more efficient than the earlier synthesis conducted by Dr. Dennie Welch. Efficency came from changing the order of fragment couplings and maintaining $C_9$ and $C_1$ at high oxidation states for as long as possible. Having $C_9$ at a ketone oxidation state resulted in chemoselectivity problems in the reduction, which were solved by a tin mediated intramolecular hydrosilylation, the most complicated application of this reaction reported to date.

## IV. Graphical Summary





## VIII. Experimental Data

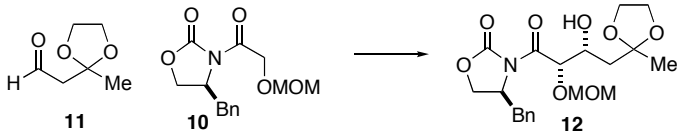
**General Information.** Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Diethyl ether and tetrahydrofuran (THF) were dried by passage through two columns of activated neutral alumina under an atmosphere of argon. Dichloromethane and toluene were dried by passage through a column of neutral alumina and a column of Q5 reactant under an atmosphere of argon. Benzene was distilled from calcium hydride under an atmosphere of nitrogen. Reagents were bought as the best grade available, subject to $^1$H NMR analysis and used without further purification unless stated otherwise. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with short wave UV light, vanillin, anisaldehyde, cerium ammonium nitrate, and/or $KMnO_4$ staining solutions followed by heating. Purification of reaction products was carried out by flash chromatography using EM Reagents silica gel 60 (230–400 mesh) according to Still's protocol,[27] eluting with solvents as indicated. All transfers from tubes to round bottom flasks were washed 3x with $CH_2Cl_2$.

Percent yields are reported for compounds that were ≥95% pure as judged by NMR, and that were pumped to a constant weight on a vacuum manifold at approximately 0.5 torr, unless otherwise states. Melting points are uncorrected. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T[^\circ C]}$ (c = g/100 mL, solvent). Infrared spectra were recorded a Perkin Elmer 1600 series FT-IR spectrometer. $^1$H NMR spectra were recorded on Varian Unity Inova600 (600 MHz) or Varian Unity Inova500 (500 MHz) spectrometers and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.27 ppm, $C_6D_6$

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

at 7.15 ppm). Data are reported as: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br: broad, app: apparent, coupling constant(s) in Hz, integration). $^{13}C$ NMR spectra were recorded on Varian Unity Inova500 (125 MHz) or Varian Mercury400 (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and $C_6D_6$ at 128.0 ppm). High-resolution mass spectra were obtained on Agilent 6210 TOF, Jeol AX-505, or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory.

**(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-(methoxymethoxy)-4-(2-methyl-1,3-dioxolan-2-yl)butanoyl)oxazolidin-2-one (12)[28]**




To a stirring solution of glycolate oxazolidinone **10** (945 mg, 3.41 mmol, 1.0 equiv), $Et_3N$ (449 mg, 4.44 mmol, 1.3 equiv), and $CH_2Cl_2$ (8.5 mL) in a flame-dried 50 mL round-bottom flask under an atmosphere of Ar, at –30 ˚C, was added $Bu_2BOTf$ (1.03 g, 3.76 mmol, 1.1 equiv) dropwise via syringe. Special care was taken to maintain the internal temperature of the reaction between –30 and –25 ˚C. The reaction was then cooled to –78 ˚C and allowed to proceed for 3 h. The reaction was warmed to 0 ˚C, held for 30 min and then cooled to –78 ˚C. Aldehyde **11** (459 mg, 3.53 mmol, 1.03 equiv), in $CH_2Cl_2$ (2.4 mL), was added to the reaction mixture dropwise via cannula. The reaction was allowed to proceed at –70 ˚C for 15.5 h and then warmed to 0 ˚C. The reaction was quenched by the dropwise addition of a 1:1 mixture of MeOH and pH 7.0 buffer (6 mL). A 30% aqueous solution of $H_2O_2$ (1.5 mL) was added dropwise, over 10 min, to the stirring reaction mixture. This hydrolysis process was allowed to proceed for 30 min.

(28) The following procedure was first carried out by Dr. Dennie Welch. I ran the procedure on the scale indicated here, and obtained the characterization data reported below.

The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a yellow oil. Purification was accomplished by flash column chromatography to yield aldol adduct **12** (894 mg, 2.19 mmol, 64% yield) as a colorless oil:

$R_f$ = 0.40 (30% acetone/hexanes, faintly UV active, stains blue in CAM);

$[\alpha]^{20}_D$ = +52 (*c* 0.90, $CHCl_3$);

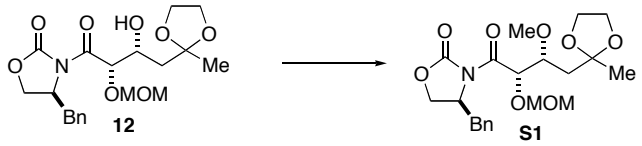
$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.38 – 7.20 (m, 5 H), 5.36 (d, *J* = 3.4 Hz, 1 H), 4.80 (d, *J* = 6.8 Hz, 1 H), 4.74 (d, *J* = 6.8 Hz, 1 H), 4.75 – 4.70 (m, 1 H), 4.35 (ddd, *J* = 10.0, 2.9, 2.7 Hz, 1 H), 4.27 – 4.22 (m, 1 H), 4.19 (dd, *J* = 9.3, 2.4 Hz, 1 H), 4.02 – 3.94 (m, 4 H), 3.43 (s, 3 H), 3.33 (dd, *J* = 13.4, 3.2 Hz, 1 H), 2.82 (dd, *J* = 13.4, 9.5 Hz, 1 H), 2.17 (s, 1 H), 2.10 (dd, *J* = 14.6, 4.9 Hz, 1 H), 2.01 (dd, *J* = 14.6, 2.4 Hz, 1 H), 1.40 (s, 3 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 170.5, 153.6, 135.4, 129.7, 129.2, 127.6, 110.1, 96.7, 76.9, 68.7, 66.8, 64.9, 64.5, 56.7, 55.7, 40.8, 37.7, 24.4;

IR (film) 3441, 2936, 2892, 1778, 1699, 1454, 1350, 1211, 1154, 1110, 918, 824, 762, 703 $cm^{-1}$;

LRMS (ES) calc for $C_{20}H_{27}NO_8$ (M + Na), 432.16, found 432.16.

**(*S*)-4-benzyl-3-((2*S*,3*R*)-3-methoxy-2-(methoxymethoxy)-4-(2-methyl-1,3-dioxolan-2-yl)butanoyl)oxazolidin-2-one (S1)[28]**




To a stirring solution of β-hydroxy ketone **12** (2.32 g, 5.67 mmol, 1.0 equiv) and $CH_2Cl_2$ (60 mL) under an atmosphere of Ar, at rt, was added 4 Å molecular sieves, proton sponge (6.0 g, 28 mmol, 5.0 equiv) and trimethyloxonium tetrafluoroborate (2.5 g, 17 mmol, 3.0 equiv). The reaction was allowed to proceed in the dark for 20 h after which time additional trimethyloxonium tetrafluoroborate (0.5 g, 3.4 mmol, 0.60 equiv) was added. After an additional 4 h, TLC indicated complete consumption of the starting material. The reaction mixture was diluted with EtOAc (100 mL) and filtered over a pad of Celite® (5 × 2 cm). The filtrate was washed with a 0.5 M aqueous solution of $NaHSO_4$ (5 × 30 mL), a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL), and brine (2 × 20 mL). The organic layer was then dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to yield viscous brown oil. Purification was accomplished via flash column chromatography (5 × 20 cm), eluting with 25% acetone/hexanes and collecting 20 mL fractions. The product containing fractions (20−40) were combined and concentrated under reduced pressure to give acetal **S1** (2.16 g, 0.510 mmol, 90% yield) as a viscous and colorless oil:

$R_f$ = 0.30 (40% acetone/hexanes, faintly UV active, stains grey in CAM);

$[\alpha]^{20}_D$ = +42.1 (*c* 1.40, $CHCl_3$);

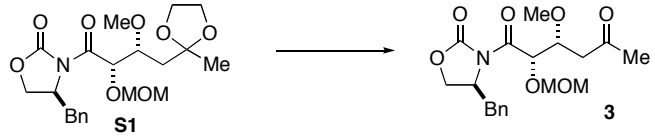
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.36 – 7.32 (m, 2 H), 7.30 – 7.23 (m, 3 H), 5.55 (d, *J* = 4.1 Hz, 1 H), 4.82 (d, *J* = 7.0 Hz, 1 H), 4.73 (d, *J* = 7.0 Hz, 1 H), 4.69 – 4.65 (m, 1 H), 4.25 – 4.16 (m, 2 H), 4.03 – 3.93 (m, 4 H), 3.87 – 3.83 (m, 1 H), 3.43 (s, 3 H), 3.37 (s, 3 H), 3.34 (dd, *J* = 13.5, 3.2 Hz 1 H), 2.81 (dd, *J* = 13.5, 9.7 Hz, 1 H), 2.21 (dd, *J* = 14.8, 4.5 Hz, 1 H), 1.92 (dd, *J* = 14.9, 6.7 Hz, 1 H), 1.38 (s, 3 H);

$^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 170.7, 153.3, 135.2, 129.5, 129.0, 127.3, 108.8, 99.4, 97.6, 77.7, 76.3, 66.4, 64.3, 58.3, 56.4, 55.8, 38.0, 37.5, 24.5 ;

IR (film) 2936, 2892, 1778, 1701, 1454, 1350, 1212, 1152, 1109, 1047, 918, 824, 762, 703 $cm^{-1}$;

Exact Mass Calc. for $C_{21}H_{29}NO_8$ $[M + Na]^+$ 446.17854, found 446.17439 (ESI)

**(2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-methoxy-2-(methoxymethoxy)-hexane-1,5-dione (3)**




To a stirring solution of acetal **S1** (2.50 g, 5.90 mmol, 1.0 equiv), acetone (59 mL), and water (5.9 mL) was added pyridinium *p*-toluenesulfonate (74 mg, 0.295 mmol, 0.050 equiv). The reaction was conducted at reflux for 8.5 h (until $^1H$ NMR of an aliquot showed complete conversion) and then allowed to cool. The acetone was removed under reduced pressure. The resulting residue was dissolved in 50% EtOAc/hexanes (100 mL), and then washed with a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL) and brine (20 mL). Removal of solvent under reduced pressure yielded ketone **3** (2.10 g, 5.54 mmol, 94%) as a colorless and viscous oil:

$R_f$ = 0.30 (40% acetone/hexanes, faintly UV active, stains faint grey in CAM);

$[\alpha]^{20}_D$ = +88.6 (*c* 0.570, $CHCl_3$);

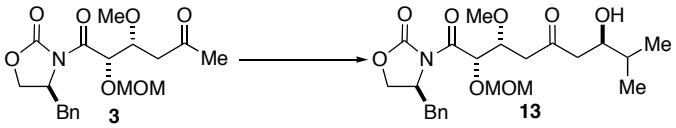
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.36 – 7.32 (m, 2 H), 7.30 – 7.24 (m, 3 H), 5.68 (d, $J$ = 5.0 Hz, 1 H), 4.78 (d, $J$ = 7.0 Hz, 1 H), 4.68 (d, $J$ = 6.7 Hz, 1 H), 4.70 – 4.66 (m, 1 H), 4.24 – 4.10 (m, 3 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 3.34 (dd, $J$ = 13.0, 3.7 Hz, 1 H), 2.88 (dd, $J$ =17.0, 3.2 Hz, 1 H), 2.82 – 2.72 (m, 2 H), 2.20 (s, 3 H) ;

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 206.5, 170.9, 153.2, 135.2, 129.4, 129.0, 127.4, 97.5, 77.1, 74.1, 66.3, 59.5, 56.3, 55.7, 44.2, 37.6, 30.9 ;

IR (film) 2934, 2831, 1778, 1711, 1604, 1453, 1391, 1350, 1212, 1153, 1111, 1046, 918, 761, 702 $cm^{-1}$;

Exact Mass Calc. for $C_{19}H_{25}NO_7$ $[M + K]^+$ 418.12626, found 418.12895 (ESI)

**(*S*)-4-benzyl-3-((2*S*,3*R*,7*R*)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-8-methyl-5-oxononanoyl)oxazolidin-2-one (13)**




Oxazolidinone ketone **3** (50 mg, 0.13 mmol, 1 eq) was dissolved in 1.3 mL toluene and triethylamine (22 µL, 0.158 mmol, 1.2 eq) was added. The solution was cooled to -78 ºC and $Cy_2BCl$ (32 µL, 0.145 mmol, 1.1 eq) was added. The solution was stirred for 1 hour and 15 minutes and then isobutyraldehyde (36 µL, 0.395 mmol, 3 eq) was added. and the reaction was stirred for 2 hours. TLC analysis (20% EtOAc/hexanes, CAM) showed complete consumption of starting material, so the reaction was quenched by the addition of 2 mL of a 1:1 mixture of pH 7 buffer and methanol. The reaction was warmed to 0 ºC and 1 mL of 30% $H_2O_{2(aq)}$ was added. After 1 hour, the reaction was diluted with 50 mL

90% EtOAc/hexanes and washed with 5 mL sat $Na_2SO_{3(aq)}$ and brine, then dried over $Na_2SO_4$. Crude $^1H$ NMR showed a 2.4:1 ratio of diastereomers, which were separated by flash chromatography (20% to 30% to 40% EtOAc/hexane). The more polar isomer is the major one.

Oxazolidinone ketone **3** (50 mg, 0.13 mmol, 1 eq) was dissolved in 1.3 mL toluene and triethylamine (22 µL, 0.158 mmol, 1.2 eq) was added. The solution was cooled to -78 ºC and 9-BBN triflate (31 µL, 0.145 mmol, 1.1 eq) was added. The orange solution was stirred for 1 hour and then isobutyraldehyde (36 µL, 0.395 mmol, 3 eq) was added and the resulting purple reaction was stirred for 2 hours. TLC analysis (20% EtOAc/hexanes, CAM) showed complete consumption of starting material, so the reaction was quenched by the addition of 2 mL of a 1:1 mixture of pH 7 buffer and methanol. The reaction was warmed to 0 ºC and 1 mL of 30% $H_2O_{2(aq)}$ was added. After 1 hour, the reaction was diluted with 50 mL 90% EtOAc/hexanes and washed with 5 mL sat $Na_2SO_{3(aq)}$ and brine, then dried over $Na_2SO_4$. Crude $^1H$ NMR showed a 4:1 ratio of diastereomers, which were separated by flash chromatography (20% to 30% to 40% EtOAc/hexane). The more polar isomer is the major one.

Analytical data for the major diastereomer is given below:

$R_f$ = 0.45 (30% acetone/ hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +76 (*c* 0.60, $CHCl_3$);

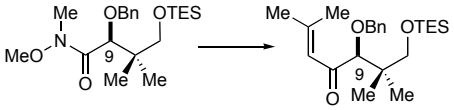
$^1H$ NMR (600 MHz, $CDCl_3$) δ 7.34 (ap. t, *J* = 7.0 Hz, 2H), 7.28 (ap. d, *J* = 7.5 Hz, 2H), 7.25 (ap. t, *J* = 7.0 Hz, 1H), 5.70 (d, *J* = 5.1 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.70- 4.65 (m, 1H), 4.23- 4.17 (m, 3H), 3.87 – 3.82 (m, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.93- 2.85 (m, 2H), 2.81- 2.74 (m, 2H), 2.62 (m, 1H), 2.61 (d, *J* = 3.1 Hz, 1H), 1.69 (sept., *J* = 6.7 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 210.0, 170.8, 153.2, 135.2, 129.4, 129.0, 127.4, 97.5, 77.1, 74.0, 72.1, 66.4, 59.5, 56.4, 55.7, 47.3, 44.1, 37.5, 33.0, 18.3, 17.2;

IR(film) 3542.4, 2960.8, 1779.4, 1708.1, 1289.3, 1350.4, 1212.1, 1111.9, 1045.8 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{33}NO_8$ $[M + Na]^+$ : 474.20984; found: 474.21113 (ESI)

**(*S*)-5-(benzyloxy)-2,6,6-trimethyl-7-(triethylsilyloxy)hept-2-en-4-one (10)[29]**




**27** **30**

To a 250 mL round-bottom flask containing 64 mL diethyl ether (64 mL) under an atmosphere of Ar, at 0 °C, was added a 1.7 M solution (pentane) of *t*–BuLi (18 mL, 30.6 mmol, 3.8 equiv), followed by the dropwise addition of 1-bromo-2-methylpropene (2.18 g, 16.2 mmol, 2 equiv) over 2 minutes. The reaction was aged for 2 h at 0 ˚C. Amide **27** (3.20 g, 8.1 mmol, 1.0 equiv) in $Et_2O$ (7 mL) was added dropwise to the reaction solution over 1 minute. After 15 min, TLC analysis indicated complete consumption of starting material. The reaction was then quenched by the rapid addition of aqueous $NaHSO_4$ (pH 2.0, 5 mL). The mixture was diluted with 10% EtOAc/hexanes (30 mL), washed with $NaHSO_4$ (pH 2.0, 4 × 5 mL), brine (2 × 5 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a pale yellow oil. Purification was accomplished by flash column chromatography (2.5 × 7 cm), eluting with 5%

(29) Dr. Dennie Welch obtained the characterization data reported below. I developed and ran the procedure that is reported below.

$Et_2O$/hexanes (50 mL) and collecting 8 mL fractions. The product containing fractions (5−22) were combined and concentrated under reduced pressure to give enone **30** (3.1 g g, 7.9 mmol, 97% yield) as a colorless oil:

$R_f$ = 0.38 (10% $Et_2O$/hex, strongly UV active, stains faint blue in CAM);

$[\alpha]^{20}_D$ = –27.1 (*c* = 2.27, $CHCl_3$);

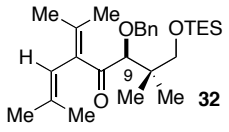
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.37 – 7.27 (m, 5 H), 6.51 – 6.48 (m, 1 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 4.35 (d, *J* = 11.2 Hz, 1 H), 3.76 (s, 1 H), 3.57 (d, *J* = 9.3 Hz, 1 H), 3.26 (d, *J* = 9.3 Hz, 1 H), 2.19 (s, 3 H), 1.92 (d, *J* = 1.0 Hz, 3 H), 0.95 (t, *J* = 8.3 Hz, 9 H), 0.92 (s, 3 H), 0.91 (s, 3 H), 0.54 – 0.62 (m, 6 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) d 203.2, 156.1, 138.6, 128.4, 127.9, 127.7, 122.3, 88.8, 72.9, 69.1, 40.2, 28.3, 21.8, 21.2, 20.4, 7.1, 4.6;

IR (thin film) 2957, 2876, 1683, 1617, 1456, 1379, 1096, 1014, 820.1, 733 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{38}O_3Si$ $[M + H]^+$ 391.26630, found 391.27174 (ESI)

**(*S*)-3-(benzyloxy)-2,2,7-trimethyl-5-(propan-2-ylidene)-1-(triethylsilyloxy))oct-6-en-4-one (32)**



**32**

$R_f$ = 0.60 (10% $Et_2O$/hexanes, strongly UV active, stains blue in CAM)

$[\alpha]^{20}_{D}$ = +160.3 (*c* 1.09, $CHCl_3$);

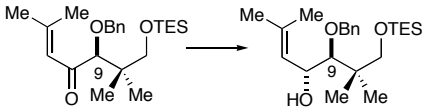
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.34- 7.24 (m, 5H), 5.78 (br. s, 1H), 4.52 (s, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.21 (d, *J* = 11.6 Hz, 1H), 3.62 (d, *J* = 9.4 Hz, 1H), 3.14 (d, *J* = 9.2 Hz, 1H), 1.97 (d, *J* = 1.8 Hz, 3H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.70 (d, *J* = 1.0 Hz, 3H), 1.52 (d, *J* = 0.7 Hz, 3H), 0.96 (ap. t, *J* = 7.9 Hz, 9H), 0.92 (s, 3H), 0.88 (s, 3H), 0.58 (ap. q, *J* = 7.9 Hz, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.8, 143.0, 138.7, 137.7, 136.6, 128.1, 127.7, 127.3, 122.0, 82.9, 71.9, 69.4, 40.7, 25.0, 23.0, 21.9, 21.4, 19.7, 19.5, 6.8, 4.5;

IR(film) 2956.5, 2876.5, 1684.9, 1455.5, 1376.4, 1093.9, 730.4 $cm^{-1}$;

Exact Mass Calc. for $C_{27}H_{44}O_3Si$ $[M + Na]^+$ : 467.29519; found: 467.29548 (ESI)

**(4*R*,5*S*)-5-(benzyloxy)-2,6,6-trimethyl-7-(triethylsiloxy)hept-2-en-4-ol (33)[28]**




To a stirring solution (0.2 M, in $Et_2O$) of $Zn(BH_4)_2$ (29 mL, 5.74 mmol, 3.00 equiv) in a flame dried 100 mL round-bottom flask under an atmosphere of Ar, at –20 ˚C, was added a solution of enone **30** (747 mg, 1.91 mmol, 1.00 equiv) in $Et_2O$ (7 mL) dropwise via cannula. The reaction was allowed to proceed 14 h, at –20 ˚C, after which time the reaction mixture was cooled to 0 ˚C. After an additional 5 h, TLC analysis showed complete consumption of the enone. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (30 mL). The mixture was diluted with 50% EtOAc/hexanes (100 mL) and the layers were separated. The aqueous layer was extracted

with an additional 50% EtOAc/hexanes (50 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was then azeotroped with MeOH (2 × 10 mL). Purification was accomplished via flash column chromatography a (2 × 15 cm), eluting with 10% $Et_2O$/hexanes (100 mL), 20% $Et_2O$/hexanes (200 mL), and collecting 10 mL fractions. The product containing fractions (15−30) were combined and concentrated under reduced pressure to give alcohol **33** (622mg, 1.58 mmol, 83% yield) as a clear and colorless oil: $R_f$ = 0.29 (20% $Et_2O$/hexanes, not UV active, stains blue in CAM);

$[\alpha]^{20}_D$ = +14.6 (*c* 0.490, $CHCl_3$);

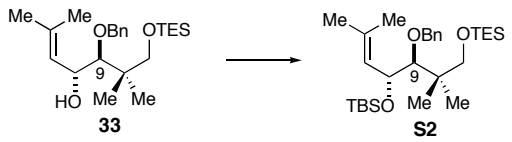
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.55 – 7.45 (m, 4 H), 7.30 – 7.20 (m, 1 H), 5.50 – 5.46 (m, 1 H), 4.76 (d, *J* = 11.2 Hz, 1 H), 4.59 (d, *J* = 11.4 Hz, 1 H), 4.55 – 4.47 (m, 1 H), 3.51 (d, *J* = 9.8 Hz, 1 H), 3.44 (d, J = 4.8 Hz, 1 H), 3.36 (d, *J* = 9.8 Hz, 1 H), 2.87 (d, *J* = 4.6 Hz, 1 H), 1.73 (d, *J* = 1.4 Hz, 3 H), 1.68 (d, *J* = 1.4 Hz, 3 H), 0.97 (t, *J* = 8.0 Hz, 9 H), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.61 (q, *J* = 8.0 Hz, 6 H) ;

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 139.5, 135.0, 128.2, 127.4, 127.2, 125.5, 87.0, 75.4, 69.6, 69.2, 40.4, 26.0, 22.2, 21.2, 18.4, 6.8, 4.3 ;

IR (film) 3438, 2957, 2876, 1454, 1239, 1091, 1006, 818, 731 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{40}O_3Si$ [M + Na] 415.26893, found 415.26799 (ESI)

**(5*R*,6*S*)-6-(benzyloxy)-10,10-diethyl-2,2,3,3,7,7-hexamethyl-5-(2-methylprop-1-enyl)-4,9-dioxa-3,10-disiladodecane (S2)[28]**




To a stirring solution of alcohol **33** (445 mg, 1.13 mmol, 1.00 equiv) and DMF (1.2 mL) in a flamed dried 5 mL round-bottom flask under an atmosphere of $N_2$, at rt, was added $Et_3N$ (237 μL, 1.69 mmol, 1.50 equiv) dropwise via syringe. The mixture was cooled to 0 ˚C and then DMAP (14 mg, 0.11 mmol, 0.10 equiv) and TBSCl (245 mg, 1.47 mmol, 1.30 equiv) were added successively. The reaction was allowed to proceed for 5 h at 0 ˚C and then warmed to rt. After an additional 20 h, TLC analysis showed complete consumption of starting material. The reaction was diluted with 25% EtOAc/hexanes (100 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (1 × 20 mL), water (4 × 20 mL), and brine (20 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by passing the orange oil over a pad of silica (3 × 5 cm), eluting 5% $Et_2O$/hexanes (50 mL). Removal of the solvent under reduced pressure yielded alkene **S2** (553 mg, 1.09 mmol, 97% yield) as a pale yellow oil:

$R_f$ = 0.95 (20% $Et_2O$/hexanes, faintly UV active, stains blue in CAM);

$[\alpha]^{20}_D$ = –7.8 (*c* 0.51, $CHCl_3$);

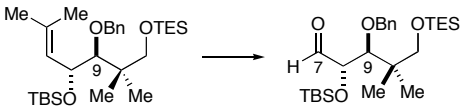
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.39 – 7.35 (m, 2 H), 7.34 – 7.30 (m, 2 H), 7.27 – 7.23 (m, 1 H), 5.52 – 5.48 (m, 1 H), 5.01 (d, *J* = 11.7 Hz, 1 H), 4.61 (dd, *J* = 9.7, 2.4 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 3.60 (d, *J* = 2.3 Hz, 1 H), 3.49 (d, *J* = 9.4 Hz, 1 H), 3.21 (d, *J* = 9.4 Hz, 1 H), 1.69 (d, *J* = 1.4 Hz, 3 H), 1.67 (d, *J* = 1.1 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.90 (s, 3 H), 0.90 (s, 9 H), 0.82 (s, 3 H), 0.61 – 0.54 (m, 6 H), 0.07 (s, 1H), 0.01 (s, 3H);

$^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 140.2, 131.5, 128.0, 127.4, 126.9, 126.4, 87.6, 75.3, 70.7, 70.0, 39.9, 25.9, 21.9, 20.6, 18.8, 18.1, 6.8, 4.5, –4.0, –4.7;

IR (film) 2956, 1462, 1249, 1093, 1040, 834, 774, 730 $cm^{-1}$;

Exact Mass Calc. for $C_{29}H_{54}O_3Si_2$ $[M + Na]^+$ 529.35037, found 529.35032 (ESI)

**(*2S,3S*)-3-(benzyloxy)-2-(tert-butyldimethylsilyloxy)-4,4-dimethyl-5 (triethylsilyloxy)pentanal (22)[28]**




Alkene **S2** (291 mg, 0.574 mmol, 1.00 equiv) was dissolved in $CH_2Cl_2$ (10 mL) and cooled to –78 ˚C. Ozone was passed through the solution until a blue color persisted, and then the reaction was sparged with $N_2$. Triphenylphosphine (150 mg, 0.574 mmol, 1.00 equiv) was added to the colorless solution, which was subsequently allowed to warm to rt. After 1 h, the solvent was removed under reduced pressure and the residue was passed through a pad of silica (3 × 5 cm) using 5% EtOAc/hexanes (50 mL) as the eluent. Removal of the solvent under reduced pressure yielded aldehyde **22** (273 mg, 0.568 mmol, 99%) as a pale yellow oil that was used immediately in the next step:

$R_f$ = 0.85 (20% $Et_2O$/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +31.5 (*c* 0.450, $CHCl_3$)

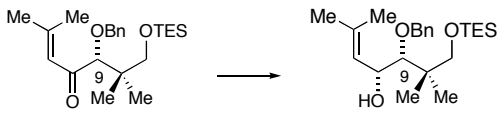
$^1$H NMR ($CDCl_3$, 600 MHz) δ 9.70 (d, $J$ = 1.6 Hz, 1 H), 7.35 – 7.30 (m, 4 H), 7.29 – 7.25 (m, 1 H), 4.85 (d, $J$ = 11.2 Hz, 1 H), 4.52 (d, $J$ = 11.2 Hz, 1 H), 4.42 – 4.40 (m, 1 H), 3.69 (d, $J$ = 1.4 Hz, 1 H), 3.47 (d, $J$ = 9.6 Hz, 1 H), 3.34 (d, $J$ = 9.6 Hz, 1 H), 0.95 (s, 3 H), 0.94 (s, 18 H), 0.93 (s, 3 H), 0.62 – 0.53 (m, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H)

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 202.0, 138.7, 128.2, 127.7, 127.4, 87.5, 79.2, 74.3, 69.0, 40.0, 25.8, 22.2, 21.0, 18.2, 6.8, 4.4, –4.6, –5.0;

IR (film) 2956, 2878, 1738, 1462, 1254, 1087, 1006, 838, 780, 731 $cm^{-1}$;

Exact Mass Calc. for $C_{26}H_{48}O_4Si_2$ $[M + H]^+$ 481.31639, found 481.31596 (ESI)

**(4*R*,5*R*)-5-(benzyloxy)-2,6,6-trimethyl-7-(triethylsilyloxy)hept-2-en-4-ol (34)**




**ent-30** **34**

Enone (*R*)- **ent-30** (500 mg, 1.28 mmol, 1 eq) was dissolved in 10 mL $CH_2Cl_2$ and cooled to -78 ºC. A 1.0 M solution of DiBAlH in toluene (2.56 mL, 2.56 mmol, 2 eq) was added and the reaction was stirred for 2 hours. After that time, TLC (30% EtOAc/hexanes) showed complete consumption of starting material. The reaction was quenched by the addition of 8 mL of saturated Rochelle's salt solution, and the biphasic mixture was stirred at ambient temperature for 2 hours. After this time, the layers were separated, the aqueous layer was extracted with 2x 10 mL $CH_2Cl_2$ and the combined organic layers were concentrated *in vacuo*. Purification of the residue by flash chromatography (10% $Et_2O$/ hexanes) allowed the isolation of 310 mg alcohol **34** (0.789 mmol, 61%) as a clear colourless oil.

$R_f$ = 0.85 (30% EtOAc/hexanes, weakly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -31.8 (*c* 3.28, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.39- 7.34 (m, 4H), 7.31- 7.27 (m, 1H), 5.36 (d sept. *J* = 8.6, 1.3 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.53 (ddd, *J* = 8.2, 5.3, 2.5 Hz, 1H), 3.52- 3.46 (m, 1H), 3.44- 3.40 (m, 1H), 3.33 (d, *J* = 2.5 Hz, 1H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.00- 0.95 (m, 9H), 0.63 (ap. q, *J* = 6.6 Hz, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.7, 133.0, 128.3, 127.9, 127.5, 127.4, 86.6, 75.9, 68.8, 67.1, 40.7, 25.8, 23.0, 21.3, 18.2, 6.7, 4.3;

IR(film) 3441.5, 2956.5, 2875.9, 1455.2, 1391.5, 1239.5, 1088.9, 1006.4, 815.5 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{40}O_3Si$ $[M + Na]^+$ : 415.26389; found: 415.25740 (ESI)

**1-(((3*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2,2,6-trimethyl-1-(triethylsilyloxy)hept-5-en-3-yloxy)methyl)benzene (S3)**


Alcohol **34** (310 mg, 0.789 mmol, 1 eq) was dissolved in 2 mL DMF and cooled to 0 ºC. Triethylamine (0.331 mL, 2.36 mmol, 3 eq) and DMAP (20 mg, 0.16 mmol, 0.2 eq) were added, followed by TBSCl (263 mg, 1.58 mmol, 2 eq). The reaction mixture was stirred for 3 hours, until TLC (30% EtOAc/hexanes) showed complete consumption of starting material. The reaction was diluted with 50 mL 50% EtOAc/hexanes and washed with 10

mL saturated $NH_4Cl_{(aq)}$, then 10 mL brine. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes) to yield 365 mg alkene **S3** (0.717 mmol, 91%) as a clear colourless oil.

$R_f$= 0.90 (30% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +3.7 (*c* 2.53, $CHCl_3$);

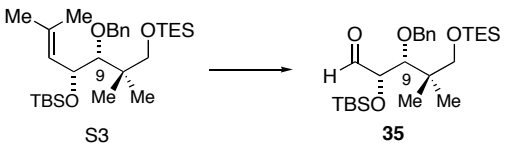
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.36 (ap. d, *J* = 8.2 Hz, 2H), 7.31 (ap. t, *J* = 7.5 Hz, 2H), 7.24 (ap. t, *J* = 8.6 Hz, 1H), 5.30 (d. sept., *J* = 1.5, 9.2 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.61 (dd, *J* = 9.2, 4.1 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 3.50 (d, *J* = 9.5 Hz, 1H), 3.31 (d, *J* = 4.1 Hz, 1H), 3.26 (d, *J* = 9.4 Hz, 1H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.65 (d, *J* = 1.3 Hz, 3H), 0.97- 0.92 (m, 9H), 0.87 (s, 9H), 0.56 (ap. q, *J* = 7.9 Hz, 6H), -0.01 (s, 3H), -0.01 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 140.0, 130.5, 128.7, 128.0, 127.1, 126.8, 86.0, 75.0, 71.1, 70.2, 40.7, 26.0, 25.7, 22.0, 21.4, 18.4, 18.2, 6.9, 4.5, -3.9, -4.5;

IR(film) 2955.8, 2876.7, 1471.9, 1388.8, 1251.4, 1083.5, 1005.1, 834.3cm$^{-1}$;

Exact Mass Calc. for $C_{29}H_{54}O_3Si_2$ $[M + Na]^+$ : 529.35037; found: 529.34978 (ESI)

**(2*S*,3*R*)-3-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-5-(triethylsilyloxy)pentanal (35)**



Alkene **S3** (150 mg. 0.296 mmol, 1 eq) was dissolved in 5 mL $CH_2Cl_2$ and cooled to -78 ºC. Ozone was bubbled through the mixture until a blue colour persisted. The reaction was then sparged with nitrogen until the blue colour was discharged. Triphenylphosphine (78 mg, 0.30 mmol, 1 eq) was added and the reaction was stirred for 30 minutes at ambient temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (10% $Et_2O$/hexanes) to yield 120 mg aldehyde **35** (0.25 mmol, 84%) as a clear colourless oil.

$R_f$= 0.85 (20% $Et_2O$/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +7.5 (*c* 1.5, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.3 Hz, 1H), 7.36- 7.25 (m, 5H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.24 (dd, *J* = 14.1, 9.3 Hz, 1H), 3.78 (d, *J* = 4.1 Hz, 1H), 3.56 (d, *J* = 9.6 Hz, 1H), 3.21 (d, *J* = 9.5 Hz, 1H), 0.97- 0.93 (m, 15H), 0.92 (s, 9H), 0.61- 0.55 (m, 6H), 0.07 (s, 3H), 0.04 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.5, 138.7, 128.2, 127.4, 127.3, 82.9, 78.6, 74.2, 69.7, 40.7, 25.8, 22.0, 21.0, 18.2, 6.8, 4.4, -4.4, -4.9;

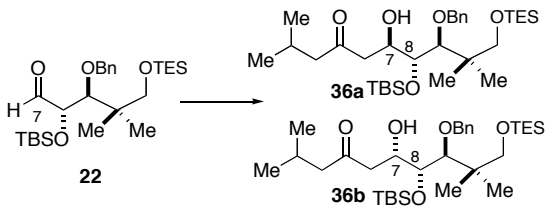
IR(film) 2955.7, 2877.0, 1734.4, 1472.3, 1361.9, 1254.4, 1093.7, 1006.2, 837.2 $cm^{-1}$;

Exact Mass Calc. for $C_{26}H_{48}O_4Si_2$ $[M + Na]^+$ : 503.29833; found: 503.29881 (ESI)

**(6*R*,7*R*,8*S*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (36a)**

**and**

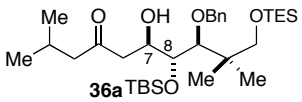
**(6*S*,7*R*,8*S*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (37b)**




Methyl isobutyl ketone (71.9 µL, 0.576 mmol, 3 eq) was dissolved in 3 mL toluene and triethylamine (78 µL, 0.557 mmol, 2.9 eq) was added. The reaction was cooled to -78 ºC and dicyclohexylboron chloride (0.122 mL, 0.557 mmol, 2.9 eq) was added. A milky white suspension formed. The reaction was stirred for 1.5 hours and then a solution of anti aldehyde **22** (92 mg, 0.19 mmol, 1 eq) was added in 1 mL toluene. After 1 hour, the reaction was quenched with the addition of 2 mL of a 1:1:1 mixture of pH 7 buffer, methanol and 30% $H_2O_{2(aq)}$. This was stirred for 2 hours at ambient temperature and then diluted with 20 mL 50% EtOAc/hexanes. The aqueous layer was separated, and the organic layer was washed with 2x5 mL saturated $Na_2S_2O_{3(aq)}$ and 5 mL brine. This was dried over $Na_2SO_4$ and concentrated *in vacuo*. Analysis of the crude mixture by $^1$H NMR showed a 3:1 ratio of diastereomers. Purification by flash chromatography on silica (2.5% EtOAc/hexanes, mixed fractions reflashed with 1% EtOAc/hexanes) allowed the seperation of two diastereomers, of which the more polar one was the major diasteromer. Analytical data for the two diastereomers is reported below:

When the corresponding reaction was attempted with 9-BBN triflate, very little conversion was observed.

**(6*R*,7*R*,8*S*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (36a)**




$R_f$= 0.50 (10% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = 12.2 (*c* 1.10, $CHCl_3$);

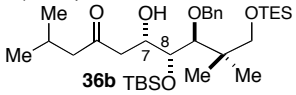
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.36- 7.27 (m, 5H), 4.91 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.33 (ap. dd, *J* = 9.8, 2.2 Hz, 1H), 4.05 (s, 1H), 3.69 (s, 1H), 3.56 (d, *J* = 9.6 Hz, 1H), 3.30 (d, *J* = 3.3 Hz, 1H), 3.21 (d, *J* = 9.6 Hz, 1H), 2.93 (dd, *J* = 17.7, 1.8 Hz, 1H), 2.62 (dd, *J* = 17.7, 10.0 Hz, 1H), 2.11 (dd, *J* = 7.3, 3.3 Hz, 2H), 1.96 (sept., *J* = 6.7 Hz, 1H), 0.99 (s, 3H), 0.97 (s, 9H), 0.96 (ap. t, *J* = 8.1 Hz, 9H), 0.90 (s, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.62- 0.57 (m, 9H), 0.15 (s, 3H), 0.13 (s, 3H)'

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 213.8, 139.3, 128.2, 127.3, 86.8, 77.2, 75.5, 69.7, 69.5, 52.6, 45.4, 40.1, 26.0, 24.6, 22.5, 22.4, 20.8, 18.2, 6.8, 4.4, -4.4, -4.5;

IR(film) 3504.0, 2955.6, 2876.3, 1701.0, 1459.0, 1406.5, 1364.0, 1252.3, 1086.9, 1015.5, 835.3 $cm^{-1}$;

Exact Mass Calc. for $C_{32}H_{60}O_5Si_2$ $[M + Na]^+$ : 603.38715; found: 603.3902 (ESI)

**(6*S*,7*R*,8*S*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (36b)**




$R_f$ = 0.52 (10% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -1.8 (*c* 3.76, $CHCl_3$);

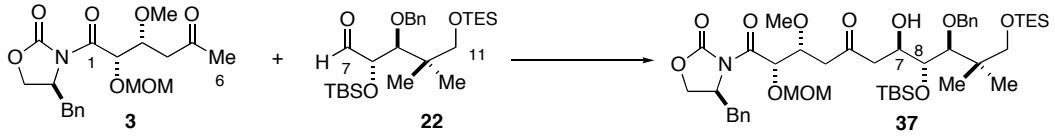
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.35- 7.27 (m, 5H), 5.08 (d, *J* = 10.7 Hz, 1H), 4.56 (d, *J* = 10.6 Hz, 1H), 4.50 (t, *J* = 6.6 Hz, 1H), 4.41 (s, 1H), 3.98 (s, 1H), 3.94 (s, 1H), 3.59 (d, *J* = 9.7 Hz, 1H), 3.21 (d, *J* = 10.5 Hz, 1H), 2.73 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.61 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.37 (dd, *J* = 16.3, 6.8 Hz, 1H), 2.28 (dd, *J* = 16.3, 6.9 Hz, 1H), 2.14 (sept. *J*= 6.7 Hz, 1H), 1.04 (s, 3H), 1.00 (s, 12H), 0.98 (ap. t, *J* = 7.9 Hz, 9H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.62 (ap. q, *J*= 8.0 Hz, 6H), 0.19 (s, 3H), 0.06 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 209.8, 138.4, 128.4, 127.6 (2 signals), 88.1, 76.6, 72.6, 70.0, 69.4, 52.6, 47.4, 39.9, 26.0, 24.2, 22.6, 22.1, 20.7, 18.2, 6.8, 4.4, -3.5, -5.0;

IR(film) 3482.4, 2956.0, 2876.7, 1710.7, 1471.6, 1409.5, 1362.5, 1254.2, 1085.7, 1006.3, 835.9 cm$^{-1}$;

Exact Mass Calc. for $C_{32}H_{60}O_5Si_2$ $[M + Na]^+$ : 603.38715; found: 603.3867 (ESI)

**(2*S*,3*R*,7*R*,8*R*,9*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-9-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-10,10-dimethyl-11-(triethylsilyloxy)undecane-1,5-dione (37)**




To a stirring solution of ketone **3** (250 mg, 0.660 mmol, 1.15 equiv), previously azeotroped with PhH (5 mL), and $PhCH_3$ (6.6 mL) in a 50 mL flame-dried round-bottom flask under an atmosphere of Ar was added $Et_3N$ (100 μL, 0.718 mmol, 1.25 equiv) dropwise via syringe. The solution was then cooled to –78 ˚C and 9-BBNOTf (140 μL, 0.660, 1.15 equiv) was added dropwise over 1 minute. The color of the solution became orange and then a deep red coloration developed over 1 h. After 1.5 h, a solution of **22** (0.574 mmol (assumed)) in $PhCH_3$ (2 mL) was added via cannula dropwise down the

inside of the flask. A deep purple solution color was observed. After an additional 1.5 h, TLC analysis indicated complete consumption of the aldehyde. The reaction was quenched with a 1:1 mixture of methanol and pH 7.0 buffer (2.0 mL) and allowed to warm to 0 ˚C. A precooled (0 ˚C) 1:1:1 mixture of methanol/ pH 7 buffer, and 30% aqueous $H_2O_2$ was added and the mixture was then allowed to warm to ambient temperature. After 15 h, the mixture was diluted with 50% EtOAc/hexanes (100 mL). The layers were separated and the organic layer was washed with water (20 mL), brine (2 × 20 mL), dried over $Na_2SO_4$, filtered, and then concentrated under reduced pressure. The resulting yellow oil was azeotroped with methanol (2 × 10 mL). Purification was accomplished with flash column chromatography (3 × 15 cm), eluting with 10% acetone/hexanes (200 mL), 20% acetone/hexanes (200 mL), and collecting 10 mL fractions. The product containing fractions (20−35) were combined and concentrated under reduced pressure to give β-hydroxy ketone **37** (395 mg, 0.460 mmol. 81%), as a 30:1 mixture of inseperable diasteromers and a viscous pale yellow oil:

$R_f$ = 0.45 (40% acetone/hexanes, faintly UV active, stains green in Anisaldehyde);

$[\alpha]^{20}_D$ = +33.4 (*c* 0.450, $CHCl_3$);

$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.39 – 7.21 (m, 10 H), 5.64 (d, *J* = 5.0 Hz, 1 H), 4.93 (d, *J* = 11.2 Hz, 1 H), 4.74 (d, *J* = 6.9 Hz, 1 H), 4.65 (d, *J* = 6.9 Hz, 1 H), 4.69 – 4.60 (m, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.39 – 4.38 (m, 1 H), 4.41 – 4.36 (m, 1 H), 4.16 (d, *J* = 4.8 Hz, 1 H), 4.19 – 4.12 (m, 1 H), 4.05 – 4.02 (m, 1 H), 3.70 – 3.70 (m, 1 H), 3.71 – 3.69 (m, 1 H), 3.53 (d, *J* = 9.6 Hz, 1 H), 3.41 – 3.38 (m, 1 H), 3.36 (s, 3 H), 3.32 (s, 3 H), 3.33 – 3.31 (m, 1 H), 3.19 - 3.13 (m, 1 H), 3.03 – 2.97 (m, 1 H), 2.85 – 2.74 (m, 2 H), 2.63 – 2.56 (m, 1 H), 0.98 – 0.94 (m, 18 H), 0.93 (s, 3 H), 0.88 (s, 3 H), 0.62 – 0.54 (m, 6 H), 0.14 (s, 3 H), 0.13 (s, 3 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 210.6, 170.7, 153.2, 139.2, 135.2, 129.4, 129.0, 128.2, 127.4, 127.4, 127.2, 97.4, 86.7, 77.2, 77.1, 76.8, 74.2, 69.8, 69.3, 66.3, 59.2, 56.3, 55.7, 46.1, 43.9, 40.1, 37.6, 26.0, 22.5, 20.8, 18.2, 6.8, 4.4, –4.3, –4.4;

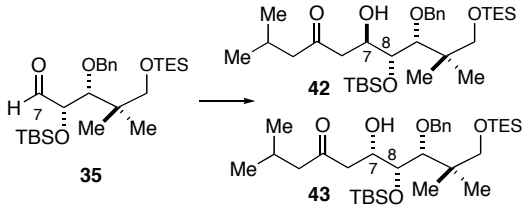
IR (thin film) 3542, 2955, 1783, 1703, 1454, 1391, 1350, 1252, 1212, 1103,1048, 836, 730, 700 $cm^{-1}$;

HRMS (ES) calc for $C_{45}H_{73}NO_{11}Si_2$ (M + Na) 882.46144, found 882.46291.

**(6*R*,7*R*,8*R*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (42)**

**and**

**(6*S*,7*R*,8*R*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (43)**

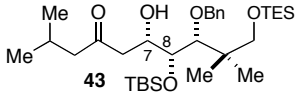



Methyl isobutyl ketone (37 μL, 0.297 mmol, 3.0 eq) was dissolved in 2 mL of toluene. Triethylamine (40 μL, 0.287 mmol, 2.9 eq) was added and the mixture was cooled to -78 ºC. To the solution was added dicyclohexylboron chloride (63 μL, 0.287 mmol, 2.9 eq) and a milky white suspension formed immediately. After stirring at -78 ºC for 30 minutes, a solution of syn aldehyde **35** (47.6 mg, 0.099 mmol, 1 eq) was added and the reaction was stirred for 2 hours. TLC analysis (20% EtOAc/hexanes, CAM) showed complete consumption of starting material, so the reaction was quenched by the addition of 2 mL of a 1:1 mixture of pH 7 buffer and methanol. The reaction was warmed to 0 ºC

and 1 mL of 30% $H_2O_{2(aq)}$ was added. After 1 hour, the reaction was diluted with 50 mL 90% EtOAc/hexanes and washed with 5 mL sat $Na_2SO_{3(aq)}$ and brine, then dried over $Na_2SO_4$. Crude $^1$H NMR showed a 1:1.4 ratio of diastereomers, which were partially separated by flash chromatography (5% EtOAc/hexanes). The more polar isomer is the major one.

Characterization Data for more polar isomer 13 mg isolated:

**(6*S*,7*R*,8*R*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (43)**




$R_f$ = 0.48 (10% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +22.7 (*c* 0.65, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.35- 7.23 (m, 5H), 4.73 (ap. d, *J* = 11.7 Hz, 1H), 4.45 (ap. d, *J* = 11.9 Hz, 1H), 4.10- 4.05 (m, 1H), 3.86 (dd, *J* = 6.0, 2.7 Hz, 1H), 3.57 (ap. d, *J* = 6.0 Hz, 1H), 3.49 (d, *J* = 9.5 Hz, 1H), 3.25 (d, *J* = 9.5 Hz, 1H), 2.69- 2.65 (m, 2H), 2.58 (ap. dd, *J* = 16.2, 4.7 Hz, 1H), 2.30 (dd, *J* = 7.0, 4.0 Hz, 2H), 2.13 (sept. *J* = 6.7 Hz, 1H), 0.96- 0.90 (m, 30H), 0.59- 0.54 (m, 6H), 0.06 (3H), 0.05 (s, 3H);

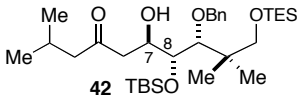
$^{13}$C NMR (125 MHz, $CDCl_3$) δ 209.4, 139.3, 128.4, 128.0, 127.3, 127.0, 80.9, 74.1, 73.5, 69.9, 69.1, 52.6, 48.0, 40.5, 29.7, 26.1, 24.3, 22.6, 21.4, 20.6, 18.2, 6.8, 4.4, -3.5, -4.9;

IR(film) 3541.9, 2955.9, 1712.0, 1471.5, 1362.7, 1254.0, 1090.9, 834.7, 731.0 $cm^{-1}$;

Exact Mass Calc. for $C_{32}H_{60}O_5Si_2$ $[M + Na]^+$ : 603.38715; found: 603.38768 (ESI)

Characterization Data for less polar isomer 11 mg isolated:

**(6*R*,7*R*,8*R*)-8-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2,9,9-trimethyl-10-(triethylsilyloxy)decan-4-one (42)**



**42**

$R_f$= 0.5 (10% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +24.7 (*c* 0.55, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.34- 7.33 (m, 4H), 7.29- 7.25 (m, 1H), 4.79 (d, *J* = 11.3 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.28- 2.19 (m, 1H), 3.91 (t, *J* = 5.1 Hz, 1H), 3.56 (d, *J* = 9.5 Hz, 1H), 3.51 (d, *J* = 4.9 Hz, 1H), 3.45 (br. s, 1H), 3.16 (d, *J* = 9.5 Hz, 1H), 2.71 (dd, *J* = 16.3, 2.7 Hz, 1H), 2.60 (dd, *J* = 16.2, 9.5 Hz, 1H), 2.36 (dd, *J* = 7.0, 5.0 Hz, 1H), 2.16 (sept., *J* = 6.7 Hz, 1H), 0.99 (s, 9H), 0.96 (d, *J* = 8.0 Hz, 3H), 0.94 (d, *J* = 7.9 Hz, 3H), 0.94 (dd, *J* = 16.6, 2.2 Hz, 2H), 0.89 (s, 15H), 0.09 (s, 3H), 0.07 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 211.2, 138.7, 130.9, 128.2, 127.3, 81.1, 74.1, 74.0, 71.0, 70.0, 52.7, 46.1, 40.7, 38.7, 30.4, 28.9, 26.1, 26.0, 25.9, 24.5, 22.6, 22.5, 21.7, 20.6, 18.2, 6.8, 4.4, -3.8, -4.6;

IR(film) 3512.0, 2956.6, 2876.6, 1708.9, 1463.5, 1362.3, 1252.2, 1089.4, 1016.2, 835.5 $cm^{-1}$;

Exact Mass Calc. for $C_{32}H_{60}O_5Si_2$ $[M + Na]^+$ : 603.38715; found: 603.38677 (ESI)

**9-BBN triflate procedure**

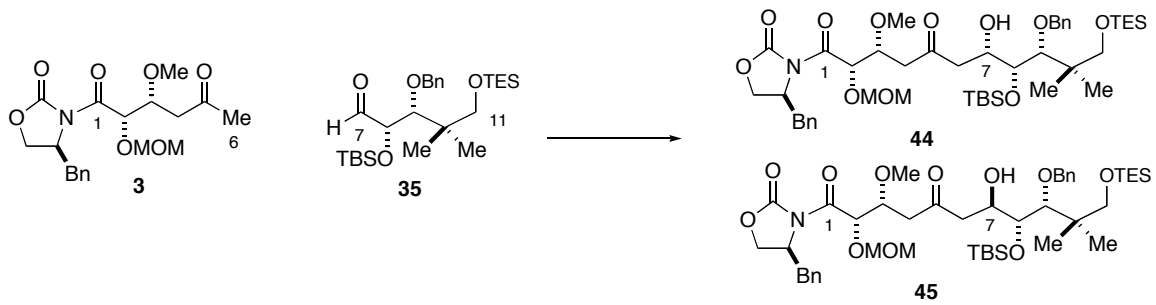
Methyl isobutyl ketone (37 μL, 0.297 mmol, 3.0 eq) was dissolved in 2 mL of toluene. Triethylamine (40 μL, 0.287 mmol, 2.9 eq) was added and the mixture was cooled to -78 ºC. To the solution was added 9-BBN triflate (61 μL, 0.287 mmol, 2.9 eq. After stirring at -78 ºC for 30 minutes, a solution of syn aldehyde **35** (47.6 mg, 0.099 mmol, 1 eq) was added and the reaction was stirred for 2 hours. TLC analysis (20% EtOAc/hexanes, CAM) showed complete consumption of starting material, so the reaction was quenched by the addition of 2 mL of a 1:1 mixture of pH 7 buffer and methanol. The reaction was warmed to 0 ºC and 1 mL of 30% $H_2O_{2(aq)}$ was added. After 1 hour, the reaction was diluted with 50 mL 90% EtOAc/hexanes and washed with 5 mL sat $Na_2SO_{3(aq)}$ and brine, then dried over $Na_2SO_4$. Crude $^1$H NMR showed a 1:9 ratio of diastereomers, which were separated by flash chromatography (5% EtOAc/hexanes). The more polar isomer **43** is the major one.

Analytical data were in accordance with that acquired for the dicyclohexylboron mediated aldol.

**(*S*)-4-benzyl-3-((2*S*,3*R*,7*S*,8*R*,9*R*)-9-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-10,10-dimethyl-5-oxo-11-(triethylsilyloxy)undecanoyl)oxazolidin-2-one (44)**

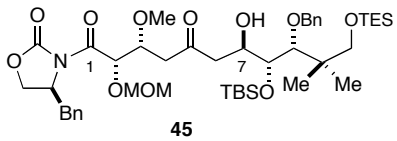
and

**(*S*)-4-benzyl-3-((2*S*,3*R*,7*R*,8*R*,9*R*)-9-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-10,10-dimethyl-5-oxo-11-(triethylsilyloxy)undecanoyl)oxazolidin-2-one (45)**




Oxazolidione ketone **5** (41 mg, 0.109 mmol, 1.1 eq) was dissolved in 2 mL of toluene. Triethylamine (15 µL, 0.109mmol, 1.1 eq) was added and the mixture was cooled to -78 ºC. To the solution was added 9-BBN triflate (23 µL, 0.109 mmol, 1.1 eq. The resulting solution turned deep orange. After stirring at -78 ºC for 40 minutes, a solution of syn aldehyde **35** (47.6 mg, 0.099 mmol, 1 eq) was added and the deep purple reaction was stirred for 1 hour and 40 minutes. TLC analysis (20% EtOAc/hexanes, CAM) showed complete consumption of starting material, so the reaction was quenched by the addition of 2 mL of a 1:1 mixture of pH 7 buffer and methanol. The reaction was warmed to 0 ºC and 1 mL of 30% $H_2O_{2(aq)}$ was added. After 1 hour, the reaction was diluted with 50 mL 90% EtOAc/hexanes and washed with 5 mL sat $Na_2SO_{3(aq)}$ and brine, then dried over $Na_2SO_4$. Crude $^1$H NMR showed a 1:2 ratio of diastereomers, which were separated by flash chromatography (20% to 30% to 40% EtOAc/hexane). The more polar isomer is the major one.

**(*S*)-4-benzyl-3-((2*S*,3*R*,7*R*,8*R*,9*R*)-9-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-10,10-dimethyl-5-oxo-11-(triethylsilyloxy)undecanoyl)oxazolidin-2-one (45)**




$R_f$= 0.15 (20% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +46.4 (*c* 0.655, $CHCl_3$);

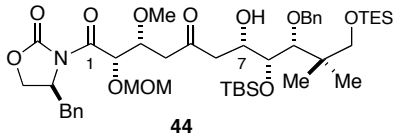
$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.36- 7.23 (m, 10H), 5.71 (d, *J* = 5.1 Hz, 1H), 4.82- 4.77 (m, 2H), 4.70- 4.64 (m, 2H), 4.46 (d, *J* = 11.3 Hz, 1H), 4.32- 3.26 (m, 1H), 4.26- 4.21 (m, 1H), 4.20- 4.15 (m, 2H), 3.89 (t, *J* =5.3 Hz, 1H), 3.54 (d, *J* = 9.5 Hz, 1H), 3.51- 3.46 (m, 1H), 3.44- 3.40 (m, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.34 (dd, *J* = 13.5, 3.4 Hz, 1H), 3.14 (d, *J* = 9.5 Hz, 1H), 2.97 (dd, *J* = 17.3, 3.0 Hz, 1H), 2.84- 2.75 (m, 2H), 2.74- 2.65 (m, 2H), 0.99 (s, 3H), 0.98 (s, 3H), 0.94 (ap. t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.61- 0.55 (m, 6H), 0.08 (s, 3H), 0.06 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 208.7, 171.0, 153.2, 138.7, 135.2, 129.5, 129.0, 128.2, 127.4, 97.5, 81.3, 76.8, 74.1 (2 signals), 74.0, 70.9, 70.1, 66.3, 59.5, 56.3, 55.7, 46.7, 44.5, 40.7, 37.6, 32.0, 29.7, 26.1, 26.0, 21.7, 20.6, 18.2, 6.8, 4.4, -3.8, -4.6;

IR(film) 3527.4, 2955.1, 1783.4, 1709.5, 1455.1, 1389.6, 1251.1, 1109.9, 835.5cm$^{-1}$;

Exact Mass Calc. for $C_{45}H_{73}NO_{11}Si_2$ $[M + Na]^+$ : 882.46144; found 882.46249 (ESI)

**(*S*)-4-benzyl-3-((2*S*,3*R*,7*S*,8*R*,9*R*)-9-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-10,10-dimethyl-5-oxo-11-(triethylsilyloxy)undecanoyl)oxazolidin-2-one (44)**




**44**

$R_f$= 0.10 (20% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +45.6 (*c* 1.26, $CHCl_3$);

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.37- 7.21 (m, 10H), 5.69 (d, *J* = 5.0 Hz, 1H), 4.78 (dd, *J* = 11.7, 6.7 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.70- 4.65 (m, 2H), 4.25- 4.15 (m, 3H), 4.09 (br. s, 1H), 3.84 (dd, *J* = 6.0, 2.8 Hz, 1H), 3.58 (d, *J* = 6.0 Hz, 1H), 3.49 (d, *J* = 9.5 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 3.33 (dd, *J* = 13.8, 3.1 Hz, 1H), 3.24 (d, *J* = 10.0 Hz, 1H), 2.89 (dd, *J* = 17.3, 3.2 Hz, 1H), 2.82- 2.78 (m, 2H), 2.76- 2.68 (m, 2H), 2.68- 2.63 (m, 2H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92- 0.90 (m, 9H), 0.90 (s, 9H), 0.60- 0.54 (m, 6H), 0.06 (s, 3H), 0.06 (s, 3H);

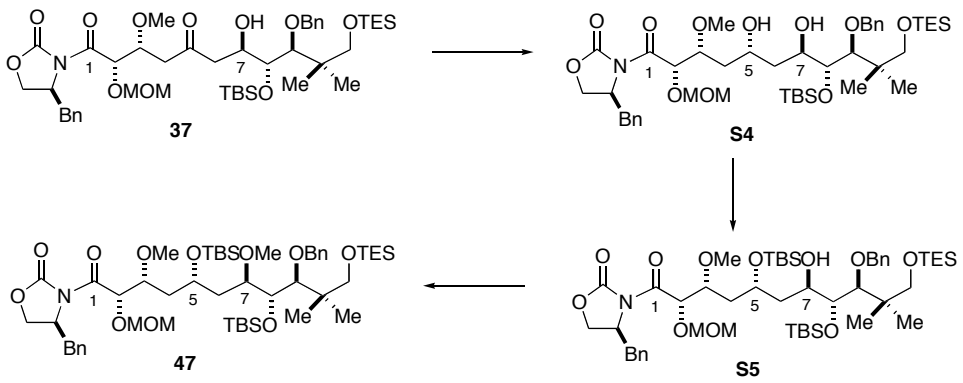
$^{13}$C NMR (125 MHz, $CDCl_3$) δ 207.2, 170.8, 153.2, 139.2, 135.2, 129.4, 129.0, 128.1, 127.4, 127.3, 127.1, 97.5, 80.9, 76.9, 74.1 (2 signals), 73.6, 69.9, 68.9, 66.3, 59.4, 56.3, 55.7, 48.5, 44.2, 40.5, 37.5, 26.1, 25.9, 21.5, 20.4, 18.2, 6.8, 4.4, -3.6, -4.9;

IR(film) 3527.5, 2955.1, 1783.1, 1710.8, 1463.5, 1390.0, 1252.9, 1109.5 $cm^{-1}$;

Exact Mass Calc. for $C_{22}H_{42}O_6Si_2$ $[M + Na]^+$ : found; (ESI)

**(*S*)-4-benzyl-3-((2*S*,3*R*,5*R*,7*R*,8*R*,9*S*)-9-(benzyloxy)-5,8-bis(*tert*-butyldimethylsilyloxy)-7-hydroxy-3-methoxy-2-(methoxymethoxy)-10,10-dimethyl-11-(triethylsilyloxy)-undecanoyl)oxazolidin-2-one (S5)[30]**

(30) The following characterization data was obtained by Dr. Dennie Welch, and the procedure was developed by him. I ran the reaction on the scale reported.




To a stirring mixture of $CH_3CN$ (28 mL) and $Me_4N(OAc)_3BH$ (3.05 g , 11.6 mmol, 5.0 equiv) in a flame-dried 10 mL round-bottom flask under an atmosphere of Ar, at rt, was added AcOH (28 mL) dropwise via syringe (solution immediately became homogeneous). The solution was cooled to –30 ˚C and β-hydroxy ketone **37** (2.01 g, 2.34 mmol, 1.0 equiv) in $CH_3CN$ (16 mL) was added dropwise via cannula down the inside of the reaction flask. TLC analysis after 24 h indicated complete consumption of starting material. The reaction was quenched by direct transfer to a vigorously stirring mixture of 50% EtOAc/hexanes (300 mL), a saturated aqueous solution of potassium sodium tartrate (150 mL), and a saturated aqueous solution of $NaHCO_3$ (150 mL). The vigorously stirring mixture was allowed to slowly warm to rt and then solid $NaHCO_3$ was added until a neutral pH was achieved. The mixture was stirred for an additional 30 min, and then the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL), brine (2 × 20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give the diol **S4** (2.1 g) as a pale yellow oil, and a 95:5 mixture of diastereomers, that was azeotroped with MeOH (2 × 15 mL) and taken onto the next reaction without further manipulation.

To a stirring solution of diol **S4** (2.34 mmol (assumed), 1.0 equiv), DMF (11 mL), and $Et_3N$ (0.65 mL, 4.6 mmol, 2.0 equiv) in a flame-dried 10 mL round-bottom flask under an atmosphere of Ar, at 0 ˚C, was added TBSCl (0.42 g, 2.8 mmol, 1.2 equiv) in

one portion. TLC analysis after 12 h, during which time the 0 ˚C bath was allowed to expire naturally, indicated complete consumption of starting material. The reaction solution was diluted with 25% EtOAc/hexanes (200 mL) and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The resulting layers were separated and the organic layer was washed with water (4 × 30 mL) then dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a brown oil (2.3 g). It was found that the overall yield of the sequence was increased if this intermediate was methylated without purification, however purification of a sample of this intermediate for characterization was accomplished by flash column chromatography (2.5 × 7 cm), eluting with 5% EtOAc/hex (50 mL), 10% EtOAc/hex (50 mL), 15% EtOAc/hex (50 mL), 20% EtOAc/hex (50 mL) and collecting 5 mL fractions. The product containing fractions (31−55) were combined and concentrated under reduced pressure to give TBS ether **S5** as a colorless oil:

$R_f$ = 0.42 (25% acetone/hexanes, faintly UV active, stains blue in CAM);

$[\alpha]^{20}_D$ = +8.2 (*c* = 1.1, $CHCl_3$);

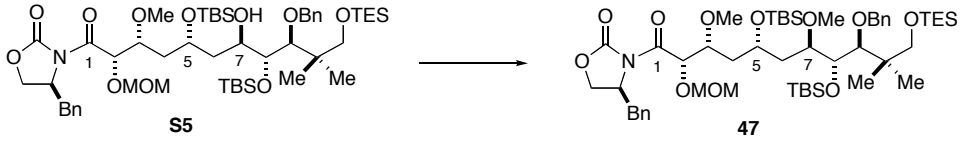
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.38 – 7.21 (m, 10 H), 5.54 (d, *J* = 5.0 Hz, 1 H), 4.99 (d, *J* = 11.7 Hz, 1 H), 4.76 (d, *J* = 7.0 Hz, 1 H), 4.65 (d, *J* = 6.7 Hz, 1 H), 4.59 (td, *J* = 9.2, 3.8 Hz, 1 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 4.21 – 4.11 (m, 3 H), 3.98 (d, *J* = 1.8 Hz, 1 H), 3.74 (s, 1 H), 3.63 (br. s., 1 H), 3.58 (d, *J* = 9.4 Hz, 1 H), 3.50 (ddd, *J* = 8.1, 2.6, 2.4 Hz, 1 H), 3.37 (s, 3 H), 3.35 (dd, *J* = 8.2, 2.1 Hz, 1 H), 3.19 (d, *J* = 9.7 Hz, 1 H), 3.11 (s, 3 H), 2.77 (dd, *J* = 13.3, 9.8 Hz, 1 H), 1.98 (dd, *J* = 14.6, 5.9 Hz, 1 H), 1.82 – 1.96 (m, 2 H), 1.79 – 1.67 (m, 2 H), 1.01 (s, 3 H), 0.97 (s, 9 H), 0.96 – 0.93 (m, 12 H), 0.87 (s, 9 H), 0.62 – 0.54 (m, 6 H), 0.15 (s, 6 H), 0.05 (s, 6 H);

$^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 171.2, 153.4, 139.7, 135.6, 129.7, 129.2, 128.3, 127.5, 127.4, 97.6, 87.4, 78.9, 78.2, 75.7, 75.6, 70.4, 70.3, 68.5, 66.4, 59.3, 56.4, 56.0, 40.3, 37.7, 37.2, 37.0, 26.2, 26.0, 23.0, 21.1, 18.4, 18.1, 7.0, 4.6, –3.9, –4.1, –4.4, –4.8;

IR (thin film) 3484, 2956, 2957, 1785, 1709, 1472, 1388, 1349, 1253, 1211, 1102, 836, 777, 734 $cm^{-1}$;

Exact Mass Calc. for $C_{51}H_{89}NO_{11}Si_3$ $[M + Na]^+$ 998.56356, found 998.56354 (ESI)

**(*S*)-4-benzyl-3-((2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-9-(benzyloxy)-5,8-bis(*tert*-butyldimethylsilyloxy)-3,7-dimethoxy-2-(methoxymethoxy)-10,10-dimethyl-11-(triethylsilyloxy)undecanoyl)-oxazolidin-2-one (47)[30]**




To a stirring solution of crude alcohol **S5** (2.3 g, 2.34 mmol (assumed)), Proton Sponge® (7.5 g, 35 mmol, 15 equiv), and $CH_2Cl_2$ (70 mL) in a flame-dried 200 mL round-bottom flask under an atmosphere of Ar, at rt, was added $Me_3OBF_4$ (2.6 g, 17 mmol, 7.5 equiv) in one portion. TLC analysis after 14 h indicated complete consumption of starting material. The reaction mixture was diluted with 20% EtOAc/hexanes (200 mL) and filtered through celite. The filtrate was washed with $NaHSO_4$ (pH 1.5, 4 × 20 mL), brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a dark amber residue. Purification was accomplished by flash column chromatography

eluting with 5% acetone/hexanes and the product containing fractions were combined and concentrated under reduced pressure to give methyl ether **47** (1.64 g, 1.66 mmol, 71% yield over 3 steps) as a colorless oil:

$R_f$ = 0.48 (30% EtOAc/hex, faintly UV active, stains blue);

$[\alpha]^{20}_D$ = +39.8 (*c* 0.55, $CHCl_3$);

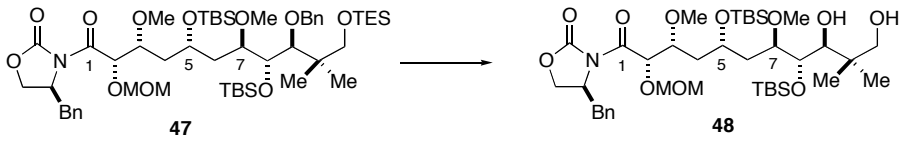
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.37 – 7.30 (m, 2 H), 7.30 – 7.19 (m, 3 H), 5.48 (d, *J* = 4.3 Hz, 1 H), 4.79 (d, *J* = 6.9 Hz, 1 H), 4.69 (d, *J* = 6.9 Hz, 1 H), 4.64 (td, *J* = 9.2, 3.8 Hz, 1 H), 4.21 – 4.14 (m, 2 H), 4.09 (t, *J* = 9.3 Hz, 1 H), 3.95 (d, *J* = 5.0 Hz, 1 H), 3.72 (d, *J* = 4.8 Hz, 1 H), 3.68 (d, *J* = 10.1 Hz, 1 H), 3.66 – 3.60 (m, 1 H), 3.43 (s, 3 H), 3.49 – 3.41 (m, 1 H), 3.39 (s, 6 H), 3.37 – 3.41 (m, 1 H), 3.35 (dd, *J* = 13.7, 3.2 Hz, 1 H), 3.07 (br. s., 1 H), 2.79 (dd, *J* = 13.4, 9.7 Hz, 1 H), 1.92 – 1.81 (m, 1 H), 1.77 (br. s., 1 H), 1.68 (d, *J* = 10.5 Hz, 1 H), 1.65 (d, *J* = 11.2 Hz, 1 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 6 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ171.2, 153.2, 140.1, 135.6, 129.7, 129.1, 128.2, 127.5, 127.4, 126.9, 97.4, 86.6, 79.8, 79.3, 76.9, 75.5, 73.2, 70.4, 66.6, 66.4, 59.7, 56.8, 56.3, 56.0, 40.6, 40.1, 37.7, 37.5, 26.3, 26.2, 22.7, 21.2, 18.5, 18.2, 7.1, 4.6, –3.7, –4.1, –4.3, –4.5;

IR (thin film) 2955, 2930, 2857, 1786, 1709, 1472, 1388, 1349, 1253, 1210, 1102, 1055, 1006, 836, 775, 734 $cm^{-1}$;

LRMS (ES) calcd for $C_{52}H_{91}NO_{11}Si_3$ $[M + Na]^+$ 1012.58, found 1012.58.

**(*S*)-4-benzyl-3-((2*S*,3*R*,5*S*,7*R*,8*S*,9*S*)-5,8-bis(*tert*-butyldimethylsilyloxy)-9,11-dihydroxy-3,7-dimethoxy-2-(methoxymethoxy)-10,10-dimethylundecanoyl)oxazolidin-2-one (48)[30]**




A 4 mL vial containing a stirring mixture of benzyl ether **47** (173 mg, 0.174 mmol, 1.0 equiv), 20% $Pd(OH)_2/C$ (24 mg, 0.0349 mmol, 0.2 equiv), and EtOAc (1 mL), at rt, was equipped with a $H_2$-filled balloon. TLC analysis after 5 h indicated complete consumption of starting material. The reaction mixture was diluted with EtOAc (10 mL) and filtered over a pad of celite. The celite pad was washed with EtOAc (20 mL). The filtrate was concentrated under reduced pressure to give a colorless residue (140 mg). Purification was accomplished by flash column chromatography (2.5 × 8 cm), eluting with 5% acetone/hex (100 mL), 7.5% acetone/hex (100 mL), 10% acetone/hex (100 mL), 12.5% acetone/hex (100 mL), 15% acetone/hex (100 mL), 17.5% acetone/hex (100 mL) and collecting 8 mL fractions. The product containing fractions (13−35) were combined and concentrated under reduced pressure to give diol **48** (108 mg, 0.131 mmol, 79% yield) as a white foam:

$R_f$ = 0.20 (20% acetone/hex, faintly UV active, stains blue);

$[\alpha]^{20}_D$ = +38.4 (*c* 1.71, $CHCl_3$);

$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.37 – 7.30 (m, 2 H), 7.30 – 7.19 (m, 3 H), 5.48 (d, *J* = 4.3 Hz, 1 H), 4.79 (d, *J* = 6.9 Hz, 1 H), 4.69 (d, *J* = 6.9 Hz, 1 H), 4.64 (td, *J* = 9.2, 3.8 Hz, 1 H), 4.21 – 4.14 (m, 2 H), 4.09 (t, *J* = 9.3 Hz, 1 H), 3.95 (d, *J* = 5.0 Hz, 1 H), 3.72 (d, *J* =

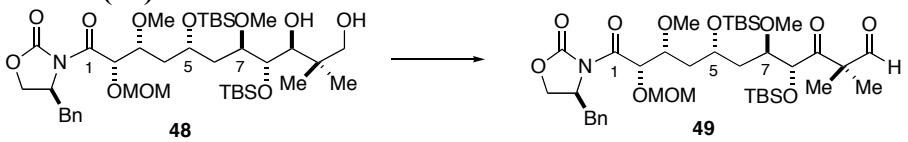
4.8 Hz, 1 H), 3.68 (d, $J$ = 10.1 Hz, 1 H), 3.66 – 3.60 (m, 1 H), 3.43 (s, 3 H), 3.49 – 3.41 (m, 1 H), 3.39 (s, 6 H), 3.41 – 3.37 (m, 1 H), 3.35 (dd, $J$ = 13.7, 3.2 Hz, 1 H), 3.07 (br. s., 1 H), 2.79 (dd, $J$ = 13.4, 9.7 Hz, 1 H), 1.92 – 1.81 (m, 1 H), 1.77 (br. s., 1 H), 1.68 (d, $J$ = 10.5 Hz, 1 H), 1.65 (d, $J$ = 11.2 Hz, 1 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 6 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ171.2, 153.4, 135.5, 129.7, 129.2, 127.6, 97.6, 82.3, 80.7, 79.1, 76.8, 73.8, 73.4, 66.7, 66.6, 59.7, 58.0, 56.4, 55.9, 39.9, 38.6, 38.1, 37.7, 26.3, 26.2, 22.5, 19.7, 18.4, 18.2, –3.2, –3.8, –4.2, –4.7;

IR (film) 3502, 2932, 1772, 1716, 1472, 1387, 1252, 1049, 836, 775 cm$^{-1}$;

Exact Mass Calc. for $C_{39}H_{71}NO_{11}Si_2$ $[M + Na]^+$ 808.44579, found 808.45366 (ESI)

**(4*R*,5*R*,7*S*,9*R*,10*S*)-11-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4,7-bis(*tert*-butyldimethylsilyloxy)-5,9-dimethoxy-10-(methoxymethoxy)-2,2-dimethyl-3,11-dioxoundecanal (49)[30]**




To a stirring solution of diol **48** (420 mg, 0.534mmol, 1.0 equiv), pyridine (2 mL), and $CH_2Cl_2$ (20 mL) in a 100 mL round-bottom flask under an atmosphere of Ar, at 0 ˚C, was added Dess-Martin periodinane (1.3 g, 2.7 mmol, 5.0 equiv) in one portion. TLC analysis after 12 h indicated complete consumption of starting material and formation of one product.[31] The reaction mixture was diluted with $CH_2Cl_2$ (10 mL), hexanes (25 mL),

(31) The eluent employed for TLC analysis of the reaction mixture was 30% EtOAc/hexanes. Under these conditions, the product aldehyde has a retention factor of 0.67. A spot presumed to be the β-hydroxy aldehyde can be observed in the first several h of the reaction and has retention factor of 0.45.

a saturated aqueous solution of $NaHCO_3$ (10 mL), and then cooled to 0 ˚C. A saturated aqueous solution of $Na_2S_2O_3$ (10 mL) was added dropwise via syringe to the stirring reaction mixture. The mixture was stirred vigorously for 30 min, diluted with 30% EtOAc/hexanes (80 mL), and then the layers were separated. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 5 mL), $H_2O$ (3 × 5 mL), brine (3 × 5 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a colorless oil that was taken onto the next reaction without further manipulation. Characterization data for aldehyde **49**:

$R_f$ = 0.67 (30% EtOAc/hexanes, eluted twice, faintly UV active, stains blue);

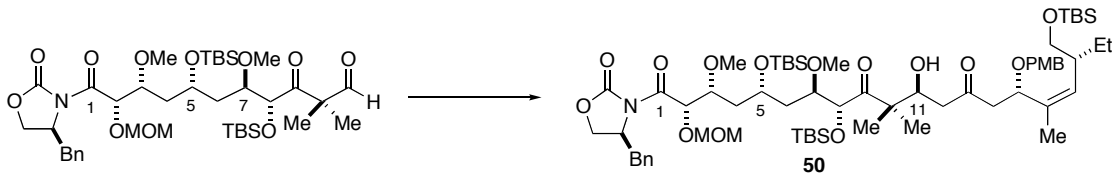
$^1$H NMR ($CDCl_3$, 600 MHz) δ 9.74 (s, 1 H), 7.39 – 7.32 (m, 2 H), 7.31 – 7.21 (m, 3 H), 5.52 (d, *J* = 4.4 Hz, 1 H), 4.80 (d, *J* = 6.7 Hz, 1 H), 4.65 (ddd, *J* = 9.7, 6.4, 2.9 Hz, 1 H), 4.48 (d, *J* = 2.6 Hz, 1 H), 4.22 – 4.16 (m, 2 H), 4.03 (t, *J* = 8.8 Hz, 1 H), 3.70 – 3.63 (m, 2 H), 3.40 (s, 3 H), 3.40 (s, 6 H), 3.42 – 3.39 (m, 1 H), 3.36 (dd, *J* = 13.6, 2.8 Hz, 1 H), 2.80 (dd, *J* = 13.3, 9.8 Hz, 1 H), 1.86 – 1.77 (m, 2 H), 1.70 (ddd, *J* = 14.1, 9.0, 2.1 Hz, 1 H), 1.44 (ddd, *J* = 14.6, 9.2, 2.3 Hz, 1 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 6 H), 0.07 (s, 3 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 210.5, 200.1, 171.2, 153.4, 135.5, 129.7, 129.1, 127.6, 97.6, 81.1, 79.5, 78.8, 76.3, 66.5, 66.4, 59.5, 58.7, 58.5, 56.5, 56.0, 39.3, 38.5, 37.7, 26.2, 20.2, 20.2, 18.5, 18.2, –3.6, –4.2, –4.3, –4.4;

Exact Mass Calc. for $C_{39}H_{67}NO_{11}Si_2$ $[M + NH_4]^+$ 799.45909, found 799.45868 (ESI)

**2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-11-hydroxy-3,7-**

**dimethoxy-15-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10,16-trimethylicos-16-ene-1,9,13-trione (50)[29]**




To a stirring solution of ketone **5** (464 mg, 1.07 mmol, 2.0 equiv), diisopropylethylamine (151 mg, 0.335 mmol, 2.2 equiv), and $Et_2O$ (10 mL) in a flame-dried 25 mL round-bottom flask under an atmosphere of Ar, at –78 ˚C, was added 9-BBN-OTf (290 mg, 1.07 mmol, 2.0 equiv) dropwise via syringe. After 1.25 h, the solution was cooled to –115 ˚C (EtOH/$N_2$) and aldehyde **49** (0.534 mmol (assumed), 1.0 equiv), in $Et_2O$ (3.0 mL), was added dropwise via cannula down the inside of the reaction vessel. The reaction was allowed to warm over 20 min to –78 ˚C, and then held at this temperature. TLC analysis after 1.5 h (total) indicated complete consumption of aldehyde **49**. The reaction was quenched by the dropwise addition of a 1:1 mixture of MeOH and pH 7.0 buffer (3 mL), then warmed to 0 ˚C. A 30% aqueous solution of $H_2O_2$ (1.5 mL) was added dropwise by glass pipette to the stirring reaction mixture. The hydrolysis process was allowed to proceed for 1 h. The mixture was diluted with 50% EtOAc/hexanes (100 mL) and the layers were separated. The organic layer was washed with a saturated aqueous solution of $Na_2S_2O_3$ (3 × 5 mL), brine (3 × 5 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a colorless oil. Purification was accomplished by flash column chromatography (2.5 × 11 cm), eluting with 5% acetone/hex (100 mL), 7.5% acetone/hex (100 mL), 10% acetone/hex (100 mL), 12.5% acetone/hex (100 mL), 15% acetone/hex (100 mL), 17.5% acetone/hex (100 mL) and collecting 8 mL fractions. The product containing fractions (34−53) were combined and concentrated under reduced pressure to give aldol adduct **50** (600 mg, 0.493 mmol, 92% yield over two steps) as an inseparable 20:1 mixture of diastereomers, and a colorless oil:

$R_f$ = 0.23 (20% acetone/hexanes, UV active, stains purple-green in anisaldehyde);

$[\alpha]^{20}_D$ = +1.0 (*c* 0.37, $CHCl_3$);

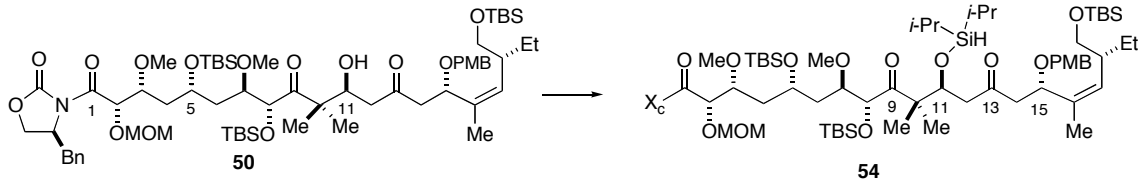
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.39 – 7.32 (m, 2 H), 7.32 – 7.24 (m, 3 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.53 (d, *J* = 4.4 Hz, 1 H), 5.19 (d, *J* = 9.8 Hz, 1 H), 4.98 (d, *J* = 2.0 Hz, 1 H), 4.79 (d, *J* = 6.8 Hz, 1 H), 4.77 – 4.83 (m, 1 H), 4.70 (d, *J* = 6.8 Hz, 1 H), 4.64 (td, *J* = 6.5, 3.2 Hz, 1 H), 4.35 (d, *J* = 10.7 Hz, 1 H), 4.25 (d, *J* = 10.3 Hz, 1 H), 4.21 – 4.13 (m, 3 H), 4.05 (t, *J* = 9.0 Hz, 1 H), 3.79 (s, 3 H), 3.70 (d, *J* = 10.3 Hz, 1 H), 3.61 (ddd, *J* = 10.4, 4.8, 2.4 Hz, 1 H), 3.52 – 3.47 (m, 2 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.44 – 3.33 (m, 1 H), 2.99 (dd, *J* = 15.6, 10.3 Hz, 1 H), 2.79 (dd, *J* = 13.7, 9.8 Hz, 1 H), 2.58 (dd, 1 H), 2.57 – 2.50 (m, 1 H), 2.48 (dd, *J* = 17.1, 10.3 Hz, 1 H), 2.27 (dd, *J* = 15.6, 2.9 Hz, 1 H), 1.73 (s, 3 H), 1.84 – 1.64 (m, 3 H), 1.60 – 1.50 (m, 1 H), 1.45 – 1.36 (m, 1 H), 1.23 (s, 3 H), 1.16 – 1.07 (m, 1 H), 1.08 (s, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.79 (t, *J* = 7.3 Hz, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 6 H), 0.03 (s, 3 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 213.4, 209.6, 171.2, 159.3, 153.4, 135.6, 134.6, 132.7, 130.7, 129.7, 129.6, 129.1, 127.5, 113.9, 97.6, 79.1, 78.7, 76.4, 75.5, 73.3, 72.9, 70.2, 67.0, 66.5, 66.3, 59.7, 57.3, 56.4, 56.0, 55.4, 51.0, 47.9, 45.8, 41.8, 39.5, 37.8, 36.6, 29.1, 26.2, 26.2, 26.1, 24.8, 22.1, 20.3, 18.7, 18.5, 18.2, 18.1, 12.0, –3.8, –4.3, –4.4, –4.4, –5.1, –5.1;

IR (film) 2955, 2929, 2856, 1785, 1710, 1462, 1385, 1250, 1100, 1050, 836, 776 $cm^{-1}$;

Exact Mass Calc. for $C_{64}H_{109}NO_{15}Si_3$ $[M + Na]^+$ 1238.6997, found 1238.7020 (ESI)

**(2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-11-(diisopropylsilyloxy)-3,7-dimethoxy-15-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10,16-trimethylicos-16-ene-1,9,13-trione (54)[28]**




To a stirring solution of β-hydroxy ketone **50** (457 mg, 0.376 mmol, 1.0 equiv), DMAP (230 mg, 1.88 mmol, 5.0 equiv), $Et_3N$ (190 mg, 1.88 mmol, 5.0 equiv), and DMF (10 mL) in a 25 mL round-bottom flask under an atmosphere of $N_2$, at 0 ˚C, was added chlorodiisopropylsilane (0.192 mL, 1.13 mmol, 3 equiv). TLC analysis after 0.5 h indicated complete consumption of starting material. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and the resulting mixture was extracted with 66% EtOAc/hexanes (3 × 100 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a pale yellow residue. Purification was accomplished by flash column chromatography (5 × 6 cm), eluting with 10% EtOAc/hexanes (200 mL) and 20% EtOAc/hexanes (300 mL). The product containing fractions were combined and concentrated under reduced pressure to give silane **54** (485 mg, 0.364 mmol, 97%) as a colorless oil:

$R_f$ = 0.74 (30% ethyl acetate/hexanes, UV active, stains brown in anisaldehyde);

$[\alpha]^{20}_D$ = 6.3 (*c* 0.57, $CHCl_3$);

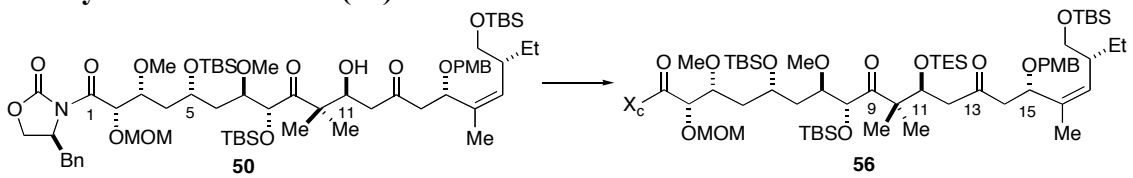
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.38 – 7.31 (m, 2 H), 7.31 – 7.24 (m, 3 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 5.53 (d, *J* = 4.7 Hz, 1 H), 5.17 (d, *J* = 10.0 Hz, 1 H),

4.93 (d, *J* = 1.8 Hz, 1 H), 4.83 (dd, *J* = 9.8, 1.9 Hz, 1 H), 4.79 (d, *J* = 6.7 Hz, 1 H), 4.69 (d, *J* = 6.7 Hz, 1 H), 4.56 – 4.59 (m, 1 H), 4.50 (dd, *J* = 6.7, 2.9 Hz, 1 H), 4.32 (d, *J* = 10.8 Hz, 1 H), 4.20 (d, *J* = 10.8 Hz, 1 H), 4.18 – 4.15 (m, 2 H), 4.13 (s, 1 H), 4.06 (t, *J* = 9.2 Hz, 1 H), 3.78 (s, 3 H), 3.75 (d, *J* = 10.8 Hz, 1 H), 3.58 (dd, *J* = 8.9, 4.5 Hz, 1 H), 3.54 – 3.43 (m, 2 H), 3.39 (s, 3 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 3.35 (d, *J* = 2.9 Hz, 1 H), 2.96 (dd, *J* = 16.4, 10.0 Hz, 1 H), 2.78 (dd, *J* = 13.3, 9.8 Hz, 1 H), 2.64 – 2.48 (m, 3 H), 2.25 (dd, *J* = 16.4, 2.1 Hz, 1 H), 1.84 – 1.71 (m, 2 H), 1.71 (s, 3 H), 1.68 – 1.51 (m, 2 H), 1.33 (s, 3 H), 1.30 – 1.20 (m, 5 H), 1.07 (s, 3 H), 1.17 – 1.05 (m, 2 H), 1.04 (t, *J* = 6.4 Hz, 7 H), 0.98 (d, *J* = 6.7 Hz, 6 H), 0.89 (br. s., 9 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.79 (t, *J* = 7.3 Hz, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 9 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 211.9, 205.7, 171.0, 158.9, 153.1, 135.4, 134.8, 132.0, 130.8, 129.5, 129.2, 128.9, 127.3, 113.6, 97.3, 78.9, 78.0, 76.1, 75.8, 74.9, 72.6, 69.9, 66.7, 66.3, 66.0, 59.5, 56.5, 56.2, 55.8, 55.2, 51.9, 48.3, 47.9, 41.5, 39.4, 37.5, 36.1, 26.0, 26.0, 25.9, 24.6, 23.1, 20.1, 18.5, 18.4, 18.0, 17.9, 17.7, 17.7, , 17.5, 17.5, 12.4, 12.3, 11.7, –4.1, –4.3, –4.3, –4.4, –5.3, –5.4;

IR (film) 2954, 2929, 2858, 1784, 1709, 1463, 1386, 1249, 1098, 1048, 834, 731 $cm^{-1}$;
Exact Mass Calc. for $C_{70}H_{123}NO_{15}Si_4$ $[M + Na]^+$ 1352.78620, found 1352.78414 (ESI)

**(*S*)-3-((2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-15-(4-methoxybenzyloxy)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-3,7-dimethoxy-2-(methoxymethoxy)-10,10,16-trimethyl-9,13-dioxo-11-(triethylsilyloxy)icos-16-enoyl)-4-benzyloxazolidin-2-one (56)**



Aldol adduct **50** (170 mg, 0.140 mmol, 1 eq) was dissolved in 6 mL $CH_2Cl_2$ and 2,6 lutidine (0.315 mL, 2.80 mmol, 20 eq) was added. The mixture was cooled to -78 °C and triethylsilyl triflate (0.16 mL, 0.70 mmol, 5.0 eq) was added. The reaction was warmed to 0 C. After 20 minutes, TLC (10% EtOAc/hexanes) showed consumption of starting materials. The reaction was quenched with 1 mL $NaHCO_{3(aq)}$. The reaction was diluted with 100 mL 50% EtOAc/hexanes, washed with 2 x 25 mL saturated $NaHCO_{3(aq)}$, with 25 mL brine, then dried over $Na_2SO_4$. The solvent was removed *in vacuo*. The residue was purified by flash chromatography to afford 130 mg (0.098 mmol, 70%) TES protected aldol **56** adduct as a clear colourless oil.

Rf= 0.85 (30% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -3.0 (*c* 1.1, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.35- 7.24 (m, 5H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.52 (d, *J* = 4.8 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 4.99 (s, 1H), 4.82 (d, *J* = 8.1 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.68- 4.60 (m, 1H), 4.31 (d, *J* = 11.0 Hz, 1H), 4.28 (d, *J* = 7.3 Hz, 1H), 4.18 (d, *J* = 10.8 Hz, 1H), 4.17- 4.14 (m, 2H), 4.03 (t, *J* = 8.9 Hz, 1H), 4.87- 4.82 (m, 1H), 3.78 (s, 3H), 3.71 (d, *J* = 10.7 Hz, 1H), 3.57 (ddd, *J* = 8.7, 4.9, 3.0 Hz, 1H), 3.51- 3.46 (m, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 3.37 (s, 3H), 2.94 (dd, *J* = 16.2, 10.0 Hz, 1H), 2.87 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.69 (d, *J* = 16.5 Hz, 1H), 2.58- 2.50 (m, 1H), 2.46 (dd, *J* = 18.6, 7.6 Hz, 1H), 2.16 (dd, *J* = 16.0, 2.0 Hz, 1H), 1.70 (s, 3H), 1.84- 1.67 (m, 2H), 1.57- 1.46 (m, 3H), 1.36 (s, 3H), 0.96 (s, 3H), 0.92 (ap. t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.64- 0.59 (m, 6H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H);

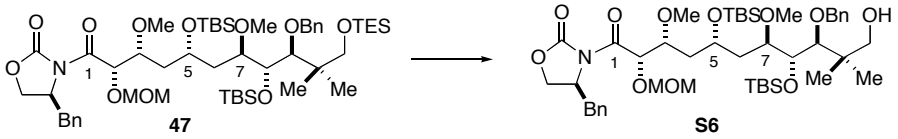
$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 212.0, 205.9, 171.0, 158.9, 153.1, 135.4, 134.8, 132.0, 130.8, 129.5, 129.2, 129.0, 127.3, 113.6, 97.3, 78.9, 77.7, 76.1, 75.8, 74.3, 72.6, 72.2, 69.9, 66.7, 66.3, 66.0, 59.6, 56.4, 56.2, 55.8, 55.2, 51.4, 48.9, 47.9, 41.5, 39.4, 37.6, 35.8, 34.7, 27.4, 26.0, 25.9, 25.2, 24.6, 23.2, 22.6, 21.1, 18.4 (2 signals), 18.0, 17.9, 11.6, 7.1, 5.1, -4.0, -4.3 (2 signals), -4.5, -5.3(2 signals);

IR(film) 2955.5, 2856.9, 1785.4, 1709.8, 1514.5, 1463.1, 1387.6, 1250.1, 1100.2, 1049.7, 1006.2, 836.4, 776.2 $cm^{-1}$;

Exact Mass Calc. for $C_{70}H_{123}NO_{15}Si_4$ $[M + Na]^+$ : 1347.83080 ; found: 1347.83036 (ESI)

i292 CSA TES cleave/ DMP oxidation. 20 mg

**(*S*)-4-benzyl-3-((2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-9-(benzyloxy)-5,8-bis(*tert*-butyldimethylsilyloxy)-11-hydroxy-3,7-dimethoxy-2-(methoxymethoxy)-10,10-dimethylundecanoyl)oxazolidin-2-one) (S6)**




Compound **47** (37 mg, 0.037 mmol) was dissolved in 2 mL 1:1 MeOH/ $CH_2Cl_2$ and cooled to 0 °C. To the mixture was added 0.9 mg CSA (0.004 mmol, 0.1 eq). TLC analysis (30% EtOAc/hexanes, CAM) showed consumption of starting material after 20 minutes. The reaction was diluted with 20 mL 50% EtOAc/hexanes and washed 2x 5mL sat $NaHCO_{3(aq)}$ then brine, then dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 20 mg alcohol **S6** (0.023 mmol, 62%) as a clear colourless oil.

$R_f$= 0.60 (30% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_{D}$ = +26.4 (*c* 0.25, $CHCl_3$);

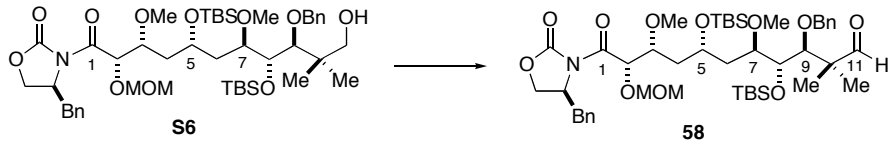
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.30- 7.22 (m, 10H), 5.45 (d, *J* = 4.5 Hz, 1H), 5.02 (d, *J* = 11.4, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.58- 4.53 (m, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.22- 4.19 (m, 1H), 4.18- 4.08 (m, 3H), 3.74 (ap. d, *J* = 10.2, 1H), 3.59 (ddd, *J* = 10.5, 4.2, 1.7 Hz, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 3.46- 3.40 (m, 1H), 2.77 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.58 (br. s, 1H), 1.92- 1.78 (m, 2H), 1.62- 1.50 (m, 2H), 1.01 (s, 6H), 0.94 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.9, 153.1, 138.6, 135.3, 129.5, 129.0, 128.3, 127.9, 127.4, 127.3, 97.2, 90.5, 79.3, 79.0, 76.6, 75.6, 73.7, 71.0, 66.4, 66.3, 59.5, 57.2, 56.2, 55.8, 40.4, 39.6, 38.1, 37.5, 29.7, 26.1, 26.0, 23.9, 21.6, 18.2, 18.0, -3.8, -4.2, -4.4, -4.5;

IR(film) 2927.7, 1786.2, 1463.2, 1254.9, 1111.9, 836.1, 775.2 $cm^{-1}$;

Exact Mass Calc. for $C_{46}H_{77}NO_{11}Si_2$ $[M + Na]^+$ : 898.4927; found: 898.49100 (ESI)

**(3*S*,4*R*,5*R*,7*S*,9*R*,10*S*)-11-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3-(benzyloxy)-4,7-bis(*tert*-butyldimethylsilyloxy)-5,9-dimethoxy-10-(methoxymethoxy)-2,2-dimethyl-11-oxoundecanal (58)**



Compound **S6** (20 mg, 0.023 mmol) was dissolved in 5 mL $CH_2Cl_2$ that had been saturated with $H_2O$ by agitation in a separatory funnel. To the mixture at ambient temperature was added Dess- Martin Periodinane (50 mg, 0.118 mmol, 5.1 eq). TLC analysis (30% EtOAc/hexanes, CAM) after 1.5 hours shows complete consumption of starting material. The reaction was quenched by dilution with 5 mL $CH_2Cl_2$ and 2 mL Hexanes, and the addition of 1 mL 10% $Na_2SO_{3(aq)}$ and 1 mL saturated $Na_2S_2O_{3(aq)}$. The biphasic mixture was stirred until both layers were clear and the layers were separated. The aqueous layer was extracted with 2x 10 mL $CH_2Cl_2$ and the combined organic layers were washed with saturated $NaHCO_{3(aq)}$ and brine then dried over $Na_2SO_4$. Concentration *in vacuo* yielded a residue that was purified by flash chromatography (20% EtOAc/hexanes) to yield 20 mg aldehyde **58** (0.023 mmol) as a clear colourless oil.

$R_f$ = 0.65 (30% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +19.5 (*c* 0.22, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.39- 7.23 (m, 10H), 5.47 (d, *J* = 4.6 Hz, 1H), 4.98 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60- 4.54 (m, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.18- 4.06 (m, 3H), 4.00 (d, *J* = 4.1 Hz, 1H), 3.70 (d, *J* = 5.5 Hz, 1H), 3.59 (ap. d, *J* = 10.5 Hz, 1H), 3.55 (ap. dd, *J* = 10.5, 4.1 Hz, 1H), 3.37 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 2.78 (dd, *J* = 13.3, 9.6 Hz, 1H), 1.90- 1.75 (m, 2H), 1.72- 1.59 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H), 0.91 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.9, 170.9, 153.1, 138.4, 135.3, 129.5, 129.0, 128.3, 128.2, 127.4, 127.3, 127.1, 97.3, 85.8, 79.4, 77.8, 76.2, 75.1, 74.1, 66.3, 59.3, 57.3, 56.2, 55.8, 50.0, 50.1, 37.9, 37.6, 29.7, 26.3, 26.0, 18.7, 18.4, 18.0, 14.1, -3.5, -4.0, -4.3, -4.4;

IR(film) 2927.5, 2855.0, 1789.5, 1714.7, 1257.5, 1104.4 $cm^{-1}$;

Exact Mass Calc. for $C_{46}H_{75}NO_{11}Si_2$ $[M + Na]^+$ : 896.47709; found: 896.4741 (ESI)

i293-i296 Aldol attempts on B benzyloxy aldehyde

**Aldol attempt with 9-BBN triflate**

Ketone **5** (40 mg, 0.092 mmol, 4 eq) was dissolved in 1 mL $Et_2O$ and cooled to -78 °C. To this solution was added Hunig's base (18 μL, 0.101 mmol, 4.4 eq) and 9-BBN triflate (19.2 μL, 0.090 mmol, 3.9 eq). The reaction was allowed to stir for 1 hour at -78 °C after which time β benzyloxy aldehyde **58** (20 mg, 0.023 mmol, 1 eq) was added dropwise in 1 mL $Et_2O$. TLC (15% EtOAc/hexanes, run 3 times, anisaldehyde) showed no consumption of aldehyde after 3 hours. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, and purfication by flash chromatography (10% to 15% EtOAc/hexanes) allowed recovery of Ketone **5** (32 mg, 80%) and aldehyde **58** (20 mg, 100%).

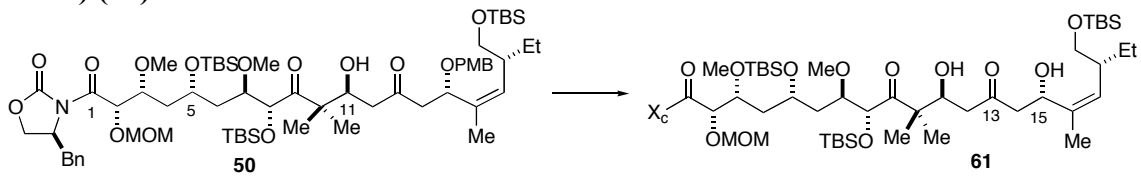
**Aldol attempt with $Bu_2BOTf$**

Ketone **5** (16 mg, 0.037 mmol, 3.2 eq) was dissolved in 1 mL $Et_2O$ and cooled to -78 °C. To this solution was added triethylamine (5.7 μL, 0.045 mmol, 3.9 eq) and dibutylboron triflate (8.75 μL, 0.036 mmol, 3.1 eq). The reaction was allowed to stir for 0.5 hour at -78 °C after which time β benzyloxy aldehyde **58** (10 mg, 0.0115 mmol, 1 eq) was added dropwise in 1 mL $Et_2O$. TLC (15% EtOAc/hexanes, run 3 times, anisaldehyde) showed no consumption of aldehyde after 3 hours. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, and $^1H$ NMR spectroscopy showed no new products derived from the aldehyde.

**Aldol attempt with $Cy_2BCl$**

Ketone **5** (24 mg, 0.0552 mmol, 4 eq) was dissolved in 1 mL $Et_2O$ and cooled to 0 °C. To this solution was added triethylamine (9 μL, 0.066 mmol, 4.8 eq) and dicyclohexylboron chloride (13 μL, 0.060 mmol, 4.4 eq). A voluminous white precipitate instantly formed. The reaction was allowed to stir for 0.5 hour at 0 °C, then was cooled to -78 ºC after which time β benzyloxy aldehyde **58** (12 mg, 0.0137 mmol, 1 eq) was added dropwise in 1 mL $Et_2O$. TLC (15% EtOAc/hexanes, run 3 times, anisaldehyde) showed no consumption of aldehyde after 1 hour. The reaction was warmed to 0 ºC for 3 hours, after which time TLC showed no progress. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, and $^1H$ NMR spectroscopy showed the aldehyde was unconsumed.

**(*S*)-3-((2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-11,15-dihydroxy-3,7-dimethoxy-2-(methoxymethoxy)-10,10,16-trimethyl-9,13-dioxoicos-16-enoyl)-4-benzyloxazolidin-2-one) (61)**




Aldol adduct **50** (42 mg, 0.0034 mmol, 1 eq) was dissolved in 4 mL $CH_2Cl_2$ and 1 mL pH 7 phosphate buffer was added. To the vigorously stirring mixture were added 3 7.8 mg aliquots of DDQ (0.034 mmol, 1.0 eq each). After 1.5 hours, NMR of an aliquot showed complete consumption of the starting material. The reaction was diluted with 50 mL 50% EtOAc/hexanes and washed with 3x10 mL saturated $NaHCO_{3(aq)}$, then brine, then dried over $Na_2SO_4$. Concentration *in vacuo* yielded a residue that was purified by flash

chromatography (10% to 25% to 40% EtOAc/hexanes) to yield 30 mg of seco acid precursor **61** (0.027 mmol, 83%) as a clear colourless oil.

$R_f$= 0.23 (20% acetone/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +7.4 (*c* 1.45, $CHCl_3$);

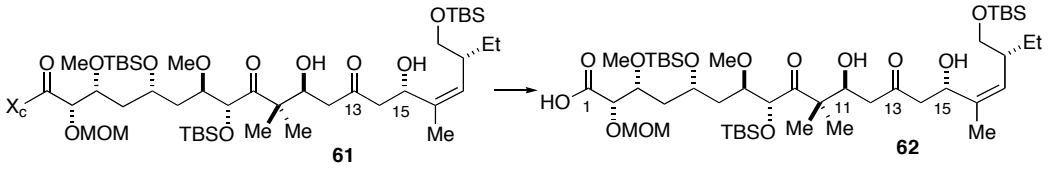
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.36- 7.24 (m, 5H), 5.52 (d, *J* = 4.7 Hz, 1H), 4.98- 4.94 (m, 3H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.66- 4.62 (m, 1H), 4.33 (d, *J* = 8.6 Hz, 1H), 4.22- 4.16 (m, 2H), 4.08- 4.02 (m, 1H), 3.72 (d, *J* = 10.4 Hz, 1H), 3.61 (ddd, *J* = 10.5, 4.7, 2.2 Hz, 1H), 3.59- 3.55 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.36 (dd, *J* = 3.2, 13.5 Hz, 1H), 3.30 (t, *J* = 9.2 Hz, 1H), 3.09 (br. s, 1H), 2.89 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.79 (dd, *J* = 13.4, 10.0 Hz, 1H), 2.63- 2.53 (m, 2H), 2.44 (dd, *J* = 6.0, 3.6 Hz, 1H), 1.83- 1.75 (m, 2H), 1.73 (s, 3H), 1.70- 1.64 (m, 1H), 1.45- 1.34 (m, 2H), 1.26 (s, 3H), 1.16 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87- 0.84 (m, 21H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 213.4, 210.7, 138.0, 131.7, 96.6, 78.5, 78.2, 76.2, 75.0, 72.6, 66.8, 66.2, 65.4, 58.8, 56.9, 56.4, 50.9, 47.3, 45.4, 41.9, 39.3, 36.6, 36.4, 31.6, 26.0, 25.9, 25.9, 25.8, 24.5, 22.0, 20.1, 18.6, 18.5, 18.3, 17.9, 14.1, 11.8, -4.1, -4.4, -4.5, -4.7 (2 signals), -5.4, -5.5;

IR(film) 3492.9, 2930.1, 2857.1 1784.9, 1709.9, 1470.0, 1389.3, 1255.2, 1104.3, 1051.5, 837.0 776.4 $cm^{-1}$;

Exact Mass Calc. for $C_{56}H_{101}NO_{14}Si_3$ $[M + Na]^+$ : 1118.64221 ; found: 1118.64533 (ESI)

**(2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-11,15-dihydroxy-3-methoxy-7-methoxy)-2-(methoxymethoxy)-10,10,16-trimethyl-9,13-dioxoicos-16-enoic acid (62)**




Seco acid precursor **61** (30 mg, 0.027 mmol, 1 eq) was dissolved in 1 mL THF and 0.2 mL $H_2O$ was added. The mixture was cooled to 0 °C and 10 drops 30% $H_2O_{2(aq)}$ were added, followed by 5 drops 1M $LiOH_{(aq)}$. After 18 hours TLC (30% EtOAc/hexanes) showed consumption of the starting material. The reaction was made neutral to $KI/KIO_3$/starch peroxide test strips by the addition of 10% $Na_2SO_{3(aq)}$ and acidified to pH paper by the addition of $NaHSO_{4(aq)}$. The mixture was extracted with 120 mL 75% EtOAc/hexanes and concentrated *in vacuo*. The residue was purified by flash chromatography (15% to 20% acetone/hexanes) to afford 19 mg seco acid **62** (0.020 mmol, 74%) as a clear colourless oil.

$R_f$= 0.55 (40% acetone/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -21 (*c* 0.95, $CHCl_3$);

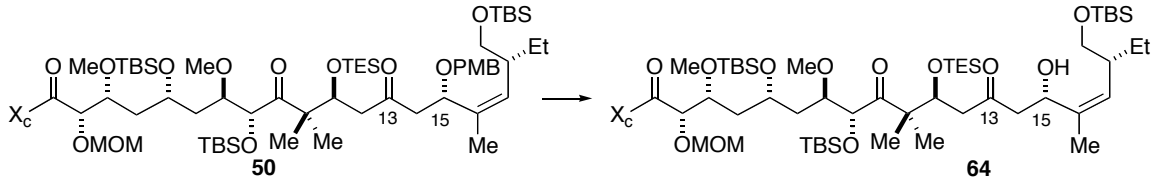
$^1$H NMR (600 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.96 (ap.d, *J* = 9.5 Hz, 2H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.31 (d, *J* = 9.8 Hz, 1H), 4.18 (d, *J* = 2.8 Hz, 1H), 4.04-3.99 (m, 1H), 3.73- 3.68 (m, 2H), 3.58 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.41- 3.40 (m, 4H), 3.28 (t, *J* = 9.1 Hz, 1H), 2.90 (dd, *J* = 16.0, 9.3 Hz, 1H), 2.62 (ap. d, *J* = 15.7 Hz, 1H), 2.59- 2.52 (m, 2H), 2.44 (dd, *J* = 16.1, 3.7 Hz, 1H), 1.87- 1.77 (m, 2H), 1.72 (s, 3H), 1.70- 1.64 (m, 1H), 1.45- 1.38 (m, 2H), 1.25 (s, 3H), 1.17 (s, 3H),

1.16- 1.09 (m, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.87- 0.83 (m, 21H), 0.07 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 213.4, 210.7, 138.0, 131.7, 96.6, 78.5, 78.2, 76.1 72.6, 66.8, 66.2, 65.4, 58.8, 56.9, 56.4, 50.9, 47.3, 45.3, 41.9, 39.3 36.6, 36.4, 31.6, 26.0, 25.8, 24.5, 22.0, 20.1, 18.6, 18.5, 18.3, 17.9, 14.1, 11.8, -4.1, -4.4, -4.7 (2 signals), -5.4 (2 signals);

IR(film) 3468.0, 2956.1, 2857.1, 1710.6, 1472.0, 1254.8, 1100.7, 836.6, 776.1cm$^{-1}$;
Exact Mass Calc. for $C_{46}H_{92}O_{13}Si_3$ $[M + Na]^+$ : 959.57379; found : 959.57364 (ESI)

**(*S*)-3-((2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-15-hydroxy-3,7-dimethoxy-2-(methoxymethoxy)-10,10,16-trimethyl-9,13-dioxo-11-(triethylsilyloxy)icos-16-enoyl)-4-benzyloxazolidin-2-one (64)**




PMB ether **56** (130 mg, 0.098 mmol, 1 eq) was dissolved in 12 mL $CH_2Cl_2$ and 4 mL pH 7 phosphate buffer was added. To the rapidly stirring biphasic mixture was added 3 22 mg aliquots of DDQ at 15 minute intervals (0.098 mmol, 1.0 eq each). After one hour, TLC showed completion so the reaction was diluted with 50 mL 50% EtOAc/hexanes and washed with 2x25 mL saturated $NaHCO_{3(aq)}$, and 25 mL brine, then dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was purified by flash

chromatography on silica gel (5% to 10% to 15% to 35% EtOAc/hexanes). Concentration yielded 90 mg of seco acid precursor **64** (0.078 mmol, 80 %) as a tan foam.

$[\alpha]^{20}_{D}$ = -5.8 (*c* 1.5, $CHCl_3$);

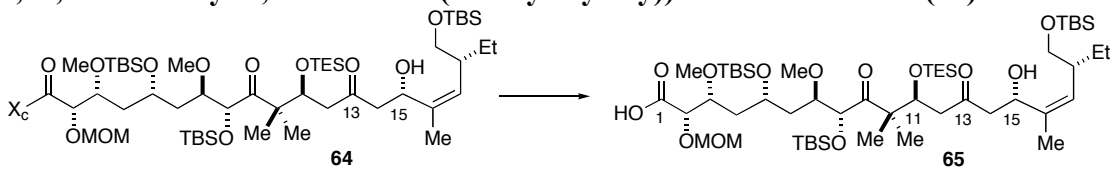
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.35- 7.23 (m, 5H), 5.52 (d, *J* = 5.0 Hz, 1H), 5.00- 4.96 (m, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* =6.7 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.65- 4.60 (m, 1H), 4.30 (dd, *J* = 7.3, 2.3 Hz, 1H), 4.17- 4.15 (m, 2H), 4.03 (ap. t, *J* = 9.3 Hz, 1H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.58 (ddd, *J* = 10.4, 4.7, 2.0 Hz, 1H), 3.51 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.38 (s, 6H), 3.37- 3.32 (m, 2H), 2.88 (d, *J* = 1.3 Hz, 1H), 2.81- 2.74 (m, 2H), 2.69 (dd, *J* = 18.1, 2.2 Hz, 1H), 2.54- 2.47 (m, 1H), 2.36 (dd, *J* = 16.7, 3.2 Hz, 1H), 1.81- 1.72 (m, 1H), 1.71 (s, 3H), 1.68- 1.62 (m, 1H), 1.50- 1.43 (m, 1H), 1.37 (s, 3H), 1.27- 1.20 (m, 1H), 1.14 – 1.07 (m, 1H), 1.00 (s, 3H), 0.94 (ap.t, *J* = 7.9 Hz, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.82 (t, *J* = 7.5 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.05 (s, 6H), 0.03 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 212.2, 208.3, 171.0, 153.1, 137.7, 135.4, 130.6, 129.5, 128.9, 127.3, 97.3, 78.9, 77.9, 76.1, 75.8, 74.0, 66.7, 66.3, 66.0, 65.1, 59.5, 56.5, 56.2, 55.8, 51.3, 48.5, 47.7, 41.9, 39.3, 37.5, 35.9, 26.0 (2 signals), 25.8, 24.5, 23.4, 20.6, 18.5, 18.3, 18.2, 17.9, 11.7, 7.1, 5.1, -4.1, -4.4, -4.5, -5.5;

IR(film) 3514.5, 2956.2, 2857.5, 1786.0, 1710.1, 1462.4, 1389.5, 1254.8, 1101.7, 1006.0, 836.8, 776.4, 736.2 $cm^{-1}$;

Exact Mass Calc. for $C_{62}H_{115}NO_{14}Si_4$ $[M + Na]^+$ : 1232.72796; found 1232.72796 (ESI)

**(2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,15*S*,18*R*,*Z*)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-15-hydroxy-3,7-dimethoxy-2-(methoxymethoxy)-10,10,16-trimethyl-9,13-dioxo-11-(triethylsilyloxy))icos-16-enoic acid (65)**




Seco acid precursor **64** (45 mg, 0.0391 mmol) was dissolved in 2 mL THF and cooled to 0 °C. To this reaction were added 10 drops $H_2O_2$ and 5 drops 1M $LiOH_{(aq)}$. The reaction was stirred at 0 °C for 12 hours after which time TLC showed completion. The reaction was made neutral to KI/$KIO_3$/starch peroxide test strips by the addition of saturated $Na_2SO_{3(aq)}$ and then acidic to pH paper by the addition of $NaHSO_{4(aq)}$. The mixture was extracted with 3x 30 mL 90% EtOAc/hexanes and washed with brine, dried over $Na_2SO_4$ then concentrated *in* vacuo. A sample from an earlier batch was purified for characterization by flash chromatography (30% EtOAc/hexanes), and the analytical data is given below, but in practice the oxazolidinone containing residue was used directly in the next step.

$R_f$= 0.15 (30% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -110 (*c* 0.95, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 5.00 (dd, *J* = 9.3, 3.2 Hz, 1H), 4.96 (s, 1H), 4.94 (d, *J* = 10.7 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.34 (dd, *J* = 7.3, 1.9 Hz, 1H), 4.19 (d, *J* = 3.2 Hz, 1H), 4.03- 3.99 (m, 1H), 3.71- 3.66 (m, 1H), 3.66 (d, *J* = 10.6 Hz, 1H), 3.52 (dd, *J* = 9.5, 5.6 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 6H), 3.33 (ap. t, *J* = 8.3 Hz, 1H), 2.80 (dd, *J* = 17.0, 9.5 Hz, 1H), 2.65 (dd, *J* = 18.0, 2.0 Hz, 1H), 2.56- 2.46 (m, 1H), 2.37 (dd, *J* = 17.0, 3.2 Hz, 1H), 1.86- 1.75 (m, 1H), 1.71 (s, 3H), 1.71- 1.64 (m, 1H), 1.49- 1.43 (m, 1H), 1.39- 1.30 (m, 1H), 1.36 (s, 3H), 1.14- 1.07 (m, 1H), 1.02 (s, 3H),

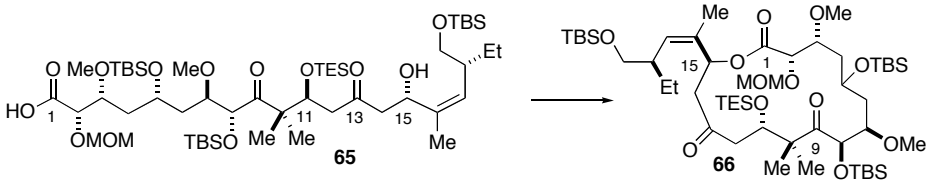
0.94 (ap. t, *J* = 8.2 Hz, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.66- 0.59 (m, 6H), 0.07 (s, 6H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 212.5, 208.0, 172.3,137.7, 130.9, 96.6, 78.6, 78.1, 75.9, 73.7, 66.7, 66.1, 65.1, 58.9, 56.7, 56.4, 51.8, 48.5, 47.6, 41.8, 39.6, 36.4, 26.0, 25.9, 25.8, 24.5, 23.4, 20.3, 18.5, 18.3 (2 signals), 17.9, 11.7, 7.1, 5.1, -4.1, -4.4(2 signals), -5.4;

IR(film) 3420, 2956.4, 2857.9, 1712.7, 1472.4, 1361.6, 1252.7, 1100.1, 1005.9, 836.6, 776.3 cm$^{-1}$;

Exact Mass Calc. for $C_{52}H_{106}O_{13}Si_4$ $[M + Na]^+$ : 1073.66027; found 1073.65953 (ESI)

**TES Keto Macrocycle 66**




The residue from the preceding reaction (0.0391 mmol, theory, 1 eq) was dissolved in 2 mL THF and to this mixture was added Hunig's base (20.4 µL, 3 theoretical eq). The reaction was stirred for 25 minutes, then 2,4,6-trichlorobenzoylchloride (15.2 µl, 0.0977 mmol, 2.5 theoretical eq) was added. The reaction was stirred for 1 hour and 40 minutes, then diluted with 20 mL toluene. This solution was added to a solution of DMAP (17 mg, 0.14 mmol, 3.5 theoretical eq) in 5 mL toluene at 60 °C at the rate of 5 mL/hr. The syringe and needle were rinsed with 5 mL toluene. The reaction was stirred for 15 hours after completion of the addition. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography over silica gel (5% EtOAc/hexanes) to afford 21 mg of macrolactone **66** (0.020 mmol, 51% over 2 steps) as a clear colourless oil.

$R_f$ = 0.90 (30% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -26.7 (*c* 0.355, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 6.04 (d, *J* = 10.1 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 4.50 (br. s, 1H), 3.96 (d, *J* = 4.5 Hz, 1H), 3.93- 3.87 (m, 1H), 3.74 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.67 (d, *J* = 10.4 Hz, 1H), 3.54 (s, 3H), 3.39 (s, 3H), 3.37 (s, 3H), 3.43- 3.30 (m, 3H), 3.06 (dd, *J* = 16.2, 11.6 Hz, 1H), 2.62- 2.55 (m, 1H), 2.54 (d, *J* = 7.0 Hz, 1H), 2.50 (ap. d, *J* = 19.0 Hz, 1H), 2.10 (dd, *J* = 16.3, 1.6 Hz, 1H), 1.79- 1.74 (m, 1H), 1.74- 1.69 (m, 1H), 1.65 (br. s, 3H), 1.59- 1.54 (m, 1H), 1.46 (t, *J* = 10.6 Hz, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 0.95 (s, 9H), 0.91 (s, 9H), 0.92- 0.87 (m, 9H), 0.89 (s, 9H), 0.77 (t, *J* = 7.5 Hz, 3H), 0.62- 0.52 (m, 6H), 0.11 (s, 6H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H);

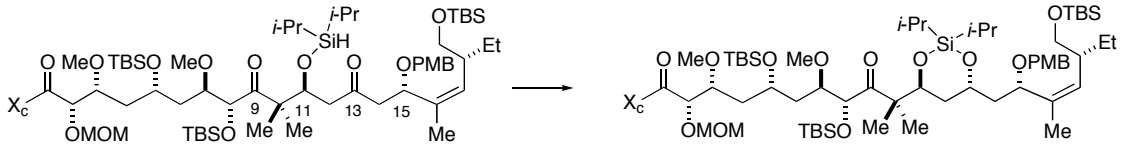
$^{13}$C NMR (125 MHz, $CDCl_3$) δ 214.4, 203.8, 168.1, 132.2, 131.0, 96.6, 79.8, 78.4, 70.7, 68.7, 67.5, 65.7, 59.4, 58.3, 56.1, 53.1, 50.8, 45.5, 41.8, 38.7, 38.5, 29.7, 26.2, 26.1, 26.0 (2 signals), 25.9, 25.7, 24.4, 24.0, 18.4, 18.2, 18.1, 17.8, 16.1, 11.9, 7.2, 5.3, 5.1, -3.7, -4.2 (2 signals), -4.9, -5.3, -5.4;

IR(film) 3413.8, 2955.7, 2857.0, 1741.5, 1724.0, 1472.0, 1383.9, 1251.6, 1100.9, 836.2 $cm^{-1}$;

Exact Mass Calc. for $C_{50}H_{100}O_{12}Si_4$ $[M + Na]^+$ : 1050.7076; found: 1055.6490 (ESI)

**(2*S*,3*R*,5*S*,7*R*,8*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5,8-bis(*tert*-butyldimethylsilyloxy)-10-((4*S*,6*R*)-6-((2*S*,5*R*,*Z*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2-(4-methoxybenzyloxy)-3-methylhept-3-enyl)-2,2-**

**diisopropyl-1,3,2-dioxasilinan-4-yl)-3,7-dimethoxy-2-(methoxymethoxy)-10-methylundecane-1,9-dione (55)**




To a solution of silane **54** (180 mg, 0.135 mmol, 1.0 equiv) and $CH_2Cl_2$ (6.0 mL) in a 25 mL round-bottom flask, at –78 ˚C, was added a 1.0 M solution ($CH_2Cl_2$) of $SnCl_4$ (13.5 μL). The reaction was allowed to proceed for 2 h and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The resulting mixture was diluted with 50% EtOAc/hexanes (45 mL) and then agitated. The resulting mixture was washed with a saturated aqueous $NaHCO_3$ (2 × 5 mL), brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give disilyloxane **55** as a clear and colorless oil that could be used without further purification (171 mg, 0.128 mg, 95%).

$R_f$ = 0.74 (30% ethyl acetate/hexanes, UV active, stains blue in CAM);

$[\alpha]^{20}_D$ = 11.0 (*c* 1.8, $CHCl_3$);

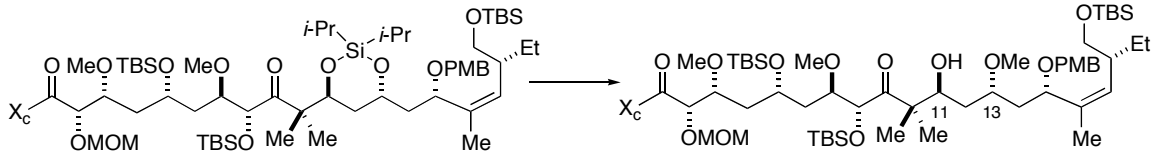
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.36 – 7.31 (m, 2 H), 7.29 – 7.26 (m, 3 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.53 (d, *J* = 5.0 Hz, 1 H), 5.32 (d, *J* = 9.4 Hz, 1 H), 4.94 (d, *J* = 2.1 Hz, 1 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.68 (d, *J* = 6.7 Hz, 1 H), 4.64 – 4.60 (m, 1 H), 4.50 (dd, *J* = 5.0, 9.7 Hz, 1 H), 4.46 (d, *J* = 10.8 Hz, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H), 4.19 (d, *J* = 11.1 Hz, 1 H), 4.17 – 4.15 (m, 2 H), 4.10 – 4.05 (m, 2 H), 3.80 (s, 3 H), 3.80 – 3.75 (m, 2 H), 3.59 – 3.56 (m, *J* = 2.1 Hz, 1 H), 3.55 – 3.51 (m, 1 H), 3.50 – 3.46 (m, 1 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 3.38 (s, 3 H), 3.37 – 3.32 (m, 2 H), 2.78 (dd, *J* = 13.5, 9.7 Hz, 1 H), 2.61 – 2.53 (m, 1 H), 2.21 – 2.15 (m, 1 H), 1.89 – 1.83 (m, 1 H), 1.81

– 1.72 (m, 1 H), 1.66 (s, 3 H), 1.64 – 1.58 (m, 2 H), 1.57 – 1.51 (m, 1 H), 1.35 – 1.30 (m, 2 H), 1.27 – 1.21 (m, 2 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 1.00 – 0.95 (m, 12 H), 0.88 (m, 18 H), 0.86 (s, 9 H), 0.84 (t, $J$ = 7.3 Hz, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H), 0.01 (s, 3 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 212.0, 171.1, 158.9, 153.1, 135.4, 134.0, 133.9, 131.3, 129.5, 129.0, 128.9, 127.3, 113.7, 97.3, 78.9, 78.1, 76.1, 75.4, 74.2, 72.5, 69.4, 68.2, 66.3, 66.3, 66.0, 59.5, 56.5, 56.2, 55.8, 55.2, 51.6, 40.7, 40.1, 39.4, 37.5, 36.0, 35.3, 26.0, 25.9, 25.8, 24.8, 21.7, 18.6, 18.4, 18.0, 17.5, 16.9, 16.9, 16.8, 16.7, 13.6, 13.1, 11.2, –4.1, –4.4, –4.5, –5.3, –5.3;

IR (film) 3478, 2954, 2929, 2856, 1783, 1708, 1514, 1301, 1153, 1097, 834, 774 cm$^{-1}$; Exact Mass Calc. for $C_{70}H_{123}NO_{15}Si_4$ $[M + Na]^+$ 1352.78620, found 1352.78414.

**(2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,13*S*,15*S*,18*R*,*Z*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-11-hydroxy-3,7,13-trimethoxy-15-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10,16-trimethylicos-16-ene-1,9-dione (69)**




To a stirring solution of **55** (116 mg, 0.0871 mmol, 1.0 equiv) and THF (2.0 mL) at 0 ˚C was added a 1.0 M solution (THF) of acetic acid (0.52 mL, 0.52 mmol, 6.0 eq), followed by 1.0 M solution (THF) of TBAF (0.52 mL, 0.52 mmol, 6.0 eq). After 1 h and 20 min, TLC indicated complete consumption of the starting material. The reaction was quenched by the addition of a saturated aqueous layer of $NH_4Cl$ (2.0 mL) and the resulting mixture

was diluted with 75% EtOAc/hexanes (40 mL). The mixture was washed with a saturate aqueous solution of $NH_4Cl$ (2 × 10 mL), brine (10 mL), and dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure (with a PhH azeotrope) to yield a gummy oil **51** (120 mg) that was immediately subjected to the next reaction.

To a stirring solution of crude diol **51** (0.0871 mmol (assumed), 1.0 equiv) and $CH_2Cl_2$ (3.0 mL) in a foil-wrapped round-bottom flask was added proton sponge® (280 mg, 1.3 mmol, 15 equiv). Trimethyloxonium tetrafluoroborate (130 mg, 0.87 mmol, 10 equiv) were then added to the reaction mixture. The reaction was allowed to proceed at rt for 30 min, after which time TLC analysis indicated complete consumption of diol **51**. The reaction was quenched by filtration through a pad of celite into a saturated aqueous solution of $NaHCO_3$ (2.0 mL). The celite pad was washed with EtOAc (10 mL). The mixture was extracted with 50% EtOAc/hexanes (50 mL). The organic layer was washed with pH 2 buffer (2 × 5 mL), brine (10 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to a brown gum. Purification was accomplished by flash column chromatography (1.5 × 12 cm), eluting with 10% EtOAc/hexanes (100 mL), 15% EtOAc/hexanes (100 mL), 20% EtOAc/hexanes (100 mL), 25% EtOAc/hexanes (100 mL) and collecting 10 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give methyl ether **69** (75mg, 0.061mmol, 70% over 2 steps) as a clear and colorless oil:

$R_f$ = 0.52 (30% ethyl acetate/hexanes, UV active, stains blue in CAM);

$[\alpha]^{20}_D$ = –5.2 (*c* 0.35, $CHCl_3$);

$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.36 – 7.30 (m, 3 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.29 – 7.22 (m, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.52 (d, *J* = 4.7 Hz, 1 H), 5.17 (d, *J* = 10.0 Hz, 1 H),

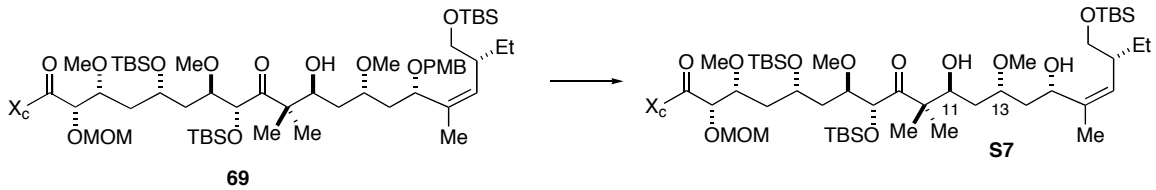
4.96 (d, *J* = 2.1 Hz, 1 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 4.68 (d, *J* = 6.7 Hz, 1 H), 4.65 – 4.61 (m, 1 H), 4.36 (d, *J* = 11.1 Hz, 1 H), 4.34 (dd, *J* = 10.0, 2.9 Hz, 1 H), 4.19 – 4.11 (m, 3 H), 4.08 – 3.99 (m, 2 H), 3.79 (s, 3 H), 3.80 – 3.78 (m, 1 H), 3.71 (d, *J* = 10.5 Hz, 1 H), 3.64 – 3.58 (m, 2 H), 3.53 – 3.47 (m, 2 H), 3.39 (s, 3 H), 3.38 (s, 6 H), 3.37 – 3.35 (m, 1 H), 3.35 – 3.31 (m, 1 H), 3.31 (s, 3 H), 2.78 (dd, *J* = 13.5, 9.7 Hz, 1 H), 2.50 – 2.43 (m, 1 H), 2.19 – 2.13 (m, 1 H), 1.81 – 1.78 (m, 2 H), 1.72 (s, 3 H), 1.69 – 1.63 (m, 1 H), 1.62 – 1.52 (m, 2 H), 1.48 – 1.43 (m, 1 H), 1.42 – 1.36 (m, 1 H), 1.27 – 1.23 (m, 1 H), 1.18 – 1.13 (m, 1 H), 1.12 (s, 3 H), 1.04 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.83 (t, *J* = 7.4 Hz, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 6 H), 0.02 (s, 6 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 213.7, 171.0, 159.1, 153.1, 135.6, 135.4, 131.7, 130.7, 129.5, 128.9, 127.3, 113.7, 97.3, 78.9, 78.4, 76.2, 74.9, 73.2, 73.0, 69.6, 66.6, 66.3, 66.1, 59.5, 56.9, 56.6, 56.2, 55.8, 55.2, 51.6, 41.4, 39.3, 37.5, 36.6, 36.3, 34.1 , 30.6, 26.0, 26.0, 25.8, 24.7, 21.5, 19.5, 18.4, 18.3, 18.0, 17.9, 11.7, –4.0, –4.5, –4.6, –4.6, –5.3, –5.4;

IR (film) 3533, 2956, 2857, 1729, 1462, 1252, 1100, 938, 836 $cm^{-1}$;

Exact Mass Calc. for $C_{65}H_{113}NO_{15}Si_3$ $[M + Na]^+$ 1254.7310, found 1254.7360.

**(2*S*,3*R*,5*S*,7*R*,8*R*,11*S*,13*R*,15*S*,18*R*,*Z*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5,8-bis(*tert*-butyldimethylsilyloxy)-18-((*tert*-butyldimethylsilyloxy)methyl)-11,15-dihydroxy-3,7,13-trimethoxy-2-(methoxymethoxy)-10,10,16-trimethylicos-16-ene-1,9-dione (S7)**



To a stirring solution of methyl ether **69** (52 mg, 0.043 mmol, 1.0 equiv), $CH_2Cl_2$ (2.0 mL), and pH 7 buffer (0.2 mL) was added a 1.0 M solution ($CH_2Cl_2$) solution of DDQ ( 172 μL, 0.172 mmol, 4.0 eq) in four portions, separated by 15 min. The reaction was allowed to proceed for 2 h, after which time TLC analysis indicated complete consumption of starting material. The reaction was diluted with 50% EtOAc/hexanes (40 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), and brine (10 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to provide an orange residue. Purification was accomplished with flash chromatography (1.5 × 12 cm), eluting with 15% EtOAc/hexanes (100 mL), 25% EtOAc/ hexanes (100 mL) and collecting 10 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to yield diol **S7** (42 mg, 0.038 mmol, 88% yield) as a clear and colorless oil:

$R_f$ = 0.45 (30% ethyl acetate/hexanes, faintly UV active, stains blue);

$[\alpha]^{20}_D$ = +14 (*c* 0.38, $CHCl_3$);

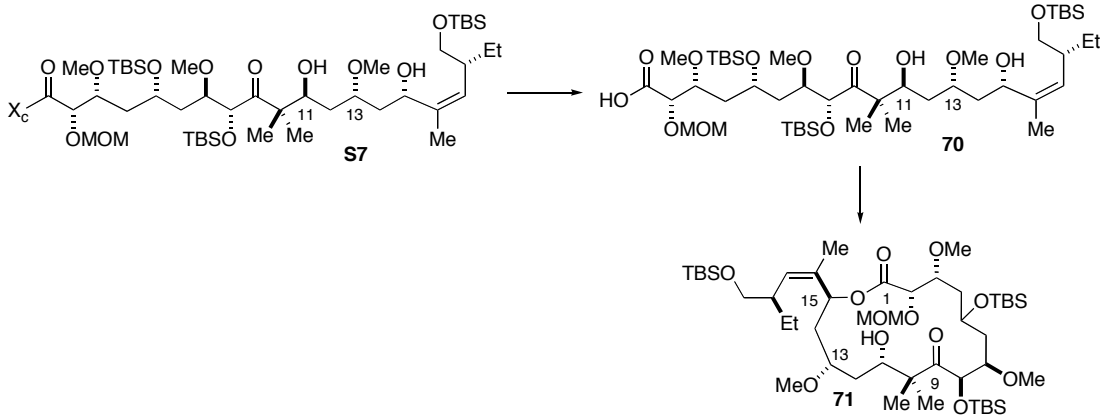
$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.36 – 7.31 (m, 2 H), 7.29 – 7.23 (m, 3 H), 5.52 (d, *J* = 5.0 Hz, 1 H), 4.96 (d, *J* = 2.3 Hz, 1 H), 4.93 (d, *J* = 10.3 Hz, 1 H), 4.79 (d, *J*=6.7 Hz, 1 H), 4.68 (d, *J* = 6.7 Hz, 1 H), 4.66 – 4.61 (m, 2 H), 4.20 – 4.14 (m, 2 H), 4.07 – 4.02 (m, 2 H), 3.73 (d, *J* = 10.5 Hz, 1 H), 3.62 – 3.57 (m, 3 H), 3.55 (dd, *J* = 9.7, 5.3 Hz, 1 H), 3.40 (s, 3 H), 3.38 (s, 6 H), 3.35 (s, 3 H), 3.35 – 3.28 (m, 2 H), 2.94 (br. s., 1 H), 2.77 (dd, *J* = 13.3, 9.8 Hz, 1 H), 2.59 – 2.52 (m, 1 H), 2.04 (s, 1 H), 2.06 – 2.00 (m, 2 H), 1.82 – 1.76 (m, 2 H), 1.73 (s, 3 H), 1.72 – 1.65 (m, 2 H), 1.65 – 1.53 (m, 2 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.14 – 1.07 (m, 1 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.83 (t, *J*=7.4 Hz, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 6 H), 0.04 (s, 6 H);

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ213.9, 171.0, 153.1, 139.4, 135.4, 130.9, 129.5, 128.9, 127.3, 97.3, 78.9, 78.5, 76.2, 75.0, 73.3, 66.9, 66.3, 66.3, 66.1, 59.4, 57.0, 57.0, 56.2, 55.8, 51.6, 41.8, 39.3, 37.5, 37.2, 36.3, 34.3, 26.0, 25.9, 25.8, 24.5, 21.4, 19.8, 18.6, 18.3, 18.2, 18.0, 11.8, –4.0, –4.5, –4.6, –4.6, –5.4, –5.4;

IR (film) 3473, 2956, 2950, 2857, 1786, 1710, 1462, 1389, 1255, 1104, 1051, 920, 837 $cm^{-1}$;

Exact Mass Calc. for $C_{57}H_{105}NO_{14}Si_3$ $[M + Na]^+$ 1134.6741, found 1134.6720 (ESI)

**(3*S*,4*R*,8*R*,9*R*,12*S*,14*S*,16*S*)-6,9-bis(*tert*-butyldimethylsilyloxy)-16-((*R*,*Z*)-4-((*tert*-butyldimethylsilyloxy)methyl)hex-2-en-2-yl)-12-hydroxy-4,8,14-trimethoxy-3-(methoxymethoxy)-11,11-dimethyloxacyclohexadecane-2,10-dione (71)**




To a stirring solution of oxazolidinone **S7** (30 mg, 0.027 mmol, 1.0 equiv) and a 4:1 mixture of THF and $H_2O$ (2.5 mL), at 0 ˚C, was added a 30% aqueous solution of $H_2O_2$ (160 μL, 1.42 mmol, 50 eq), followed by a 1.0 M aqueous solution of LiOH (108 μL, 0.108 mmol, 4 equiv.). TLC analysis after 1 h indicated complete consumption of starting material. A saturated aqueous solution of $Na_2SO_3$ was cautiously added dropwise until complete consumption of $H_2O_2$, as judged by KI/starch paper. A 1.0 M aqueous solution of $NaHSO_4$ was then added until the mixture was at pH 2.0. The mixture was

extracted with EtOAc (3 × 25 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure (with the aid of a PhH azeotrope) to give a clear and colorless residue (30 mg) that was used without further manipulation in the next reaction.[32]

To a stirring solution of a portion of the residue (21 mg, 0.019 mmol, 1.0 equiv) and THF (1 mL) was added Hunig's base (8.2 μL, 0.048 mmol, 2.5 equiv) followed by 2,4,6-trichlorobenzoyl chloride (6.2 μL, 0.040 mmol, 2.1 equiv). The reaction was allowed to proceed for 5 h, after which time TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with $PhCH_3$ (5 mL) and added over 10 h to a solution of DMAP (7.0 mg, 0.057 mmol, 3.0 eq) in $PhCH_3$ (15 mL), at 60 ˚C. The reaction was allowed to proceed for 30 h, after which time TLC analysis indicated complete consumption of the seco-acid.[33] The solvent was removed under reduced pressure to yield a yellow residue. Purification was accomplished with flash column chromatography (1 × 7 cm), eluting with 10% EtOAc/hexanes. The product containing fractions were combined and concentrated to give macrolactone **71** (12 mg, 0.013 mmol, 68% corrected yield over 2 steps) as a clear and colorless oil:

$R_f$ = 0.74 (30% ethyl acetate/hexanes, not UV active, stains blue);

$[\alpha]^{20}_D = -53$ (*c* 0.50, $CHCl_3$);

(32) A single attempt to purify the crude mixture on Davisil® column using an EtOAc/$H_2O$/MeOH/ acetone (10:1:1:1) solvent system resulted in cleavage of the MOM group.

(33) A TLC analysis of the intermediate seco-acid shows a retention factor of 0.53 with an eluent of 25% EtOAc/acetone. During the formation of the mixed anhydride, TLC analysis shows disappearance of the spot corresponding to the seco-acid and formation of a less polar spot with a retention factor 0.65 in 30% EtOAc/hexanes. Upon injection into the DMAP solution in toluene, the spot corresponding to the seco-acid reappears on TLC analysis and gradually disappears as the reaction progresses.

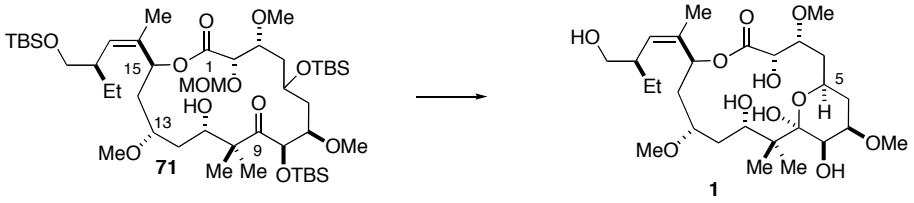
$^{1}$H NMR ($CDCl_3$, 600 MHz) δ 5.89 – 5.85 (m, 1 H), 5.08 (d, *J* = 10.0 Hz, 1 H), 4.72 (s, 1 H), 4.67 – 4.64 (m, 2 H), 4.16 (d, *J* = 4.4 Hz, 1 H), 4.00 – 3.95 (m, 1 H), 3.76 – 3.72 (m, 1 H), 3.72 (dd, *J* = 10.0, 3.8 Hz, 1 H), 3.67 – 3.60 (m, 2 H), 3.54 – 3.47 (m, 1 H), 3.44 (s, 3 H), 3.40 – 3.38 (m, 1 H), 3.38 (s, 6 H), 3.37 (s, 3 H), 2.60 – 2.53 (m, 1 H), 2.02 – 1.94 (m, 2 H), 1.91 – 1.83 (m, 1 H), 1.81 – 1.73 (m, 1 H), 1.72 – 1.66 (m, 1 H), 1.68 (s, 3 H), 1.65 – 1.59 (m, 1 H), 1.58 – 1.54 (m, 1 H), 1.54 – 1.45 (m, 2 H), 1.40 (s, 3 H), 1.23 (s, 3 H), 1.23 – 1.15 (m, 2 H), 0.91 (s, 9 H), 0.88 (s, 9 H), 0.88 (s, 9 H), 0.85 (t, *J* = 7.5 Hz, 3 H), 0.10 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ;

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 216.5, 168.8, 133.7,130.7, 96.0, 75.3, 70.3, 66.3, 65.4, 78.5, 76.0, 75.3, 70.3, 66.3, 65.4, 57.5, 57.2, 57.2, 56.1, 50.7, 41.5, 37.4, 37.3, 36.6, 35.9, 26.0, 25.9, 25.8, 24.4, 22.1, 18.3, 18.3, 18.2, 17.9, 11.8,–4.3, –4.3, –4.5, –5.0, –5.3, –5.4;

IR (film) 353.9, 2956.2, 2857.3, 1729.7, 1462.5, 1384.1, 1252.7, 1154.4, 1099.7, 938.4, 938.4, 836.2 $cm^{-1}$;

Exact Mass Calc. for $C_{47}H_{94}O_{12}Si_3$ $[M + Na]^+$ 957.5951, found 957.5947.

**Peloruside A (1)**




To a stirring mixture of macrolactone **71** (4.5 mg, 0.0048 mmol, 1.0 equiv) and MeOH (1.5 mL), 0 ˚C, was added an aqueous solution of 4 N HCl (1.5 mL) dropwise over 5 minutes. The reaction was allowed to proceed at 0 ˚C for 1 h, and then at rt for 2 h. The

reaction mixture was neutralized with a saturated aqueous solution of $NaHCO_3$ and the extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford a yellow residue. Purification was accomplished with flash column chromatography, eluting with EtOAc (50 mL), 25% acetone/EtOAc (50 mL), 50% EtOAc/acetone (50 mL), 75% acetone/EtOAc (50 mL), the last of which which eluted the product from the column. Concentration of the product containing fractions yielded a light yellow oil which was lyophilized using PhH and subsequently triturated with hexanes to yield peloruside A **1** as a fluffy white powder (1.7 mg, 0.0032 mmol, 66%);

$[\alpha]^{20}_{D} = +16$ (*c* 0.30, $CH_2Cl_2$)

$^1$H NMR ($CDCl_3$, 600 MHz) 6.75 (br s, 1 H), 5.69 (d, *J*= 10.6 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.85 – 4.95 (m, 1H), 4.53 (br d, *J* = 8.1 Hz, 1H), 4.43 (s, 1H), 4.29 – 4.21 (m, 2H), 4.03 (s, 1H), 4.02 – 3.95 (m, 1H), 3.82 (ddd, J = 11.5, 5.1, 3.0 Hz, 1H), 3.69 – 3.61 (m, 1H), 3.48 (s, 3H), 3.39 (s, 3H), 3.35 (m, 1H), 3.31 (s, 3H), 2.97 (br s, 1H), 2.70 (d, *J* = 9.3 Hz, 1H), 2.55 – 2.65 (m, 1H), 2.27 (br s, 1H), 2.19 – 2.09 (m, 2H), 1.97 – 2.09 (m, 2H), 1.82 – 1.73 (m, 2H), 1.68 (d, *J* = 1.0 Hz, 1H), 1.50 – 1.57 (m, 1H), 1.47 – 1.40 (m, 2H), 1.18- 1.15 (m, 1H), 1.13 (s, 3H), 1.10, (s, 3H), 0.86 (t, *J* = 7.5 Hz, 3H)

δ $^{13}$C NMR ($CDCl_3$, 125 MHz) 173.9, 136.1, 131.2, 101.9, 78.3, 78.0, 76.0, 73.9, 70.9, 70.3, 67.0, 63.5, 59.1, 56.1, 55.7, 43.6, 43.4, 35.7, 34.2, 33.9, 32.6, 31.7, 24.7, 20.9, 17.4, 15.7, 12.3

δ IR (film) 3441, 2924, 2854, 1739, 1455, 1386, 1155, 1085 $cm^{-1}$

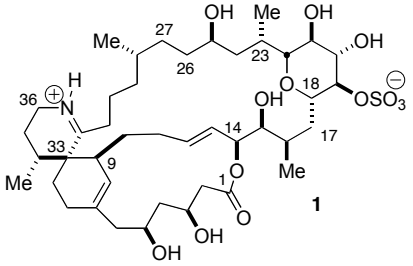
Exact Mass Calc. for $C_{27}H_{48}O_{11}$ [M + Na] 571.3094, found 571.3096 (ESI)

# *Chapter 3*

## Introduction to Spiro–prorocentrimine

### I. Isolation and Structural Determination of Spiro–prorocentrimine

Spiro-prorocentrimine (**1**) is a spiro-iminium toxin that was isolated from cultures of an unknown species of algae, from a strain designated *Prorocentrum* PM08. Another member of the *Prorocentrum* genus, *Prorocentrum lima,* has been a rich source of non spiro-iminium containing toxins such as okadaic acid. The algal specimens were isolated from seaweed from a coral reef in Taiwan.[1]




**1**

**Figure 3.1** Structure of spiro-prorocentrimine.

Extraction and chromatography of 100 L of a culture of *Prorocentrum sp*. PM08 provided 3 mg of spiro-prorocentrimine. The structure was determined by a single crystal X-ray structure, with a final R-value of 0.0859. Multidimensional NMR studies supported the configuration around the spiro-iminium and pyran moieties. The absolute configuration of spiro-prorocentrimine is unknown. From the structure in Figure 3.1, notable structural features involve an iminium bearing spirocycle, the presence of a 15 membered lactone, and the presence of a 23 membered macrocyclic ether, a sulfated

(1) Lu, C.-K.; Lee, G.-H.; Huang, R.; Chou, H.-N. *Tetrahedron Lett.* **2001**. *42*, 1713-1716.

pyran moiety and a potentially fragile allylic ester. Because of the presence of the sulfate and iminium, the molecule is zwitterionic. Spiro-prorocentrimine is toxic, with an i.p. $LD_{99}$ in mice of 2.5 mg/kg. This is much lower than the toxicity of related compounds.[2]

## II. Approaches to Other Aza-Spirocyclic Natural Products

No published approaches other than our own exist to spiro-prorocentrimine. However, several elegant and informative approaches to molecules related to spiro-prorocentrimine have been made. A detailed summary of these approaches up to 2005 and 2007 may be found in the PhD theses of Dr. Anna Chiu and Dr. George Borg respectively. The purpose of the following section is to briefly summarize the most important approaches relevant to our own approach. Representative molecules in the spiro-iminium family with similar aza-spirocyclic regions are shown in figure 3.2.

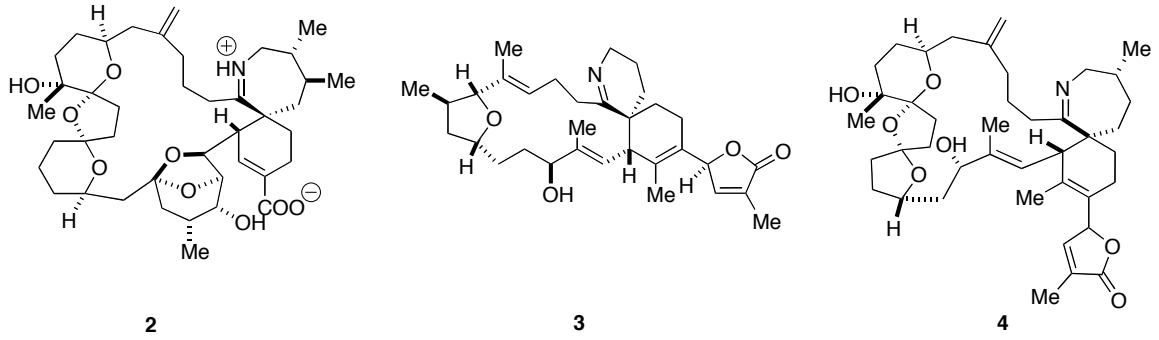


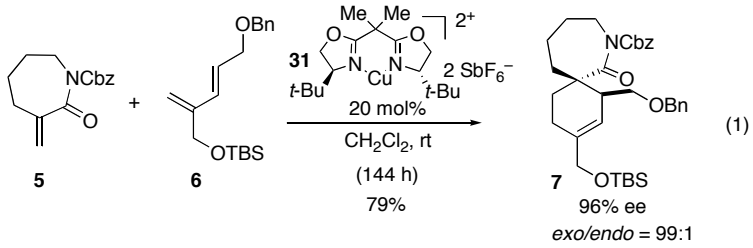

**Figure 3.2** Representative members of spiro-iminium family

Total syntheses of pinnatoxin A (**2**) have been reported by Kishi, Nagasawa, Hirama, Hashimoto and Zakarian. Gymnodimine (**3**) has been recently synthesized by Romo, while Kishi also described an elegant approach. No synthesis of a member of the spirolide family, represented above by spirolide A (**4**) has yet been reported, however

(2) Alberto Otero, M.-J. C.; Atanassova, M.; Vieites, J. M.; Cabado, A. G. *Chem. Res. Toxicol.,* **2011**, *24*, 1817- 1829. No human intoxications from spiro-imine toxins have been reported: EFSA Panel on Contaminants in the Food Chain. *EFSA Journal* . **2010**, *6*, 1628- 1667. DOI: 10.2903/j.efsa.2012.1628

efforts towards this target have been published by Zakarian, Brimble, Ishihara, and our group. [3]

An approach to the spiro-iminium cores of natural products pioneered by Murai and subsequently enhanced and employed our group, the Romo group, and the Brimble group involves Diels- Alder reactions of exo-methylene lactams with E dienes. A representative example is shown in Equation 3.1. CBz protected caprolactam **5** reacts with diene **6**, promoted by a cationic copper BOX catalyst. Diels–Alder adduct **7** is obtained in high ee, with an excellent exo-endo ratio.[4]




The exo transition state is presumably favoured since it would minimize a steric interaction between the diene and the BOX catalyst, which would be bound to the imide oxygens.

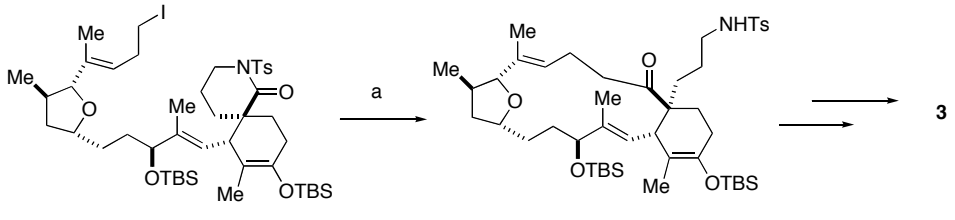
A pitfall to this strategy appears to be the elaboration of the lactam adjacent to a quaternary centre in the product to a ketone oxidation state (the iminium). While unsuccessful attempts employed by our group are described in the next section, the only successful strategy that has been reported is a substrate specific Barbier type

(3) a) Stivala, C. E.; Zakarian, A. *Org. Lett.* **2009**, *11*, 839- 842. b) Brimble, M. A.; Crimmins, D.; Trzoss, M. *ARKIVOC*, **2005,** 39- 52**.** C) Ishihara, J.; Ishizaka, T.; Suzuki, T.; Hatakeyama, S. *Tetrahedron. Lett.* **2004**, *45*, 7855- 7858.

(4) The structures in this scheme, equation or figure are adapted from ones drawn by Dr. Anna Chiu, with her permission.

macrocyclization employed by Romo in his total synthesis of gymnodimine (scheme 3.1).[5]

**Scheme 3.1**




**8** **9**

a) *t*-BuLi, $Et_2O$, r.t.

Iodide **8**, synthesized by a Diels–Alder reaction employing a tosyl-lactam,[6] was exposed to *t*-BuLi, which resulted in intramolecular addition of the resulting alkyllithium to the tosyl-lactam to form compound **9** in 51- 65% yield. This was subsequently elaborated to gymnodimine in 7 steps. This sort of reaction did also work in an intermolecular fashion, but a general solution to functionalize neopentyl lactams to iminiums is still unknown as this reaction failed on similar substrates in both Romo's earlier efforts towards gymnodimine and our own efforts toward spiro-prorocentrimine.[6]

In his original isolation paper for Pinnatoxin A, Uemura proposed that Pinnatoxin A arose from an intramolecular Diels–Alder reaction between a diene and an enone in compound **10**, followed by a condensation on **11** to form the iminium in Pinnatoxin A (Figure 3.3).[7] An updated biosynthetic proposal is made both in sections III of this chapter and in Appendix A.

(5) a) Kong, K.; Romo, D.; Lee, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 7402- 7405. b) Kong, K.; Moussa, Z.; Lee, C.; Romo, D. *J. Am. Chem. Soc.,* **2011**, *133*, 19844- 19856.

(6) Kong, K.; Moussa, Z.; Romo, D. *Org. Lett.,* **2005***, 7,* 5127- 5130.

(7) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.-Z.; Chen, H.-S. *J. Am. Chem. Soc.,* **1995**, *117*, 1155- 1156.

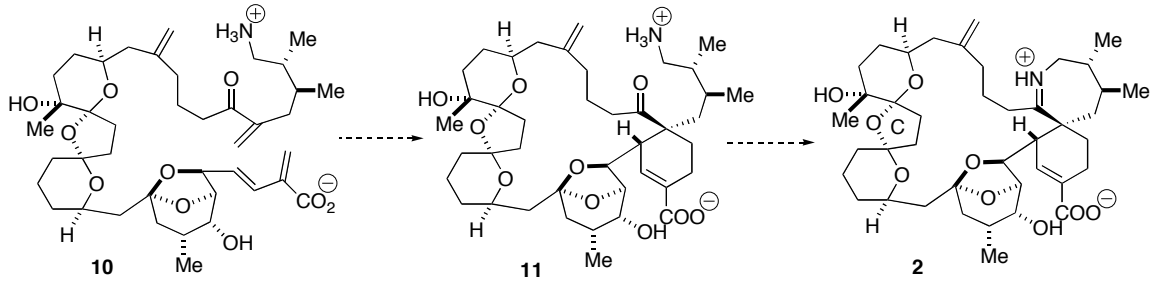
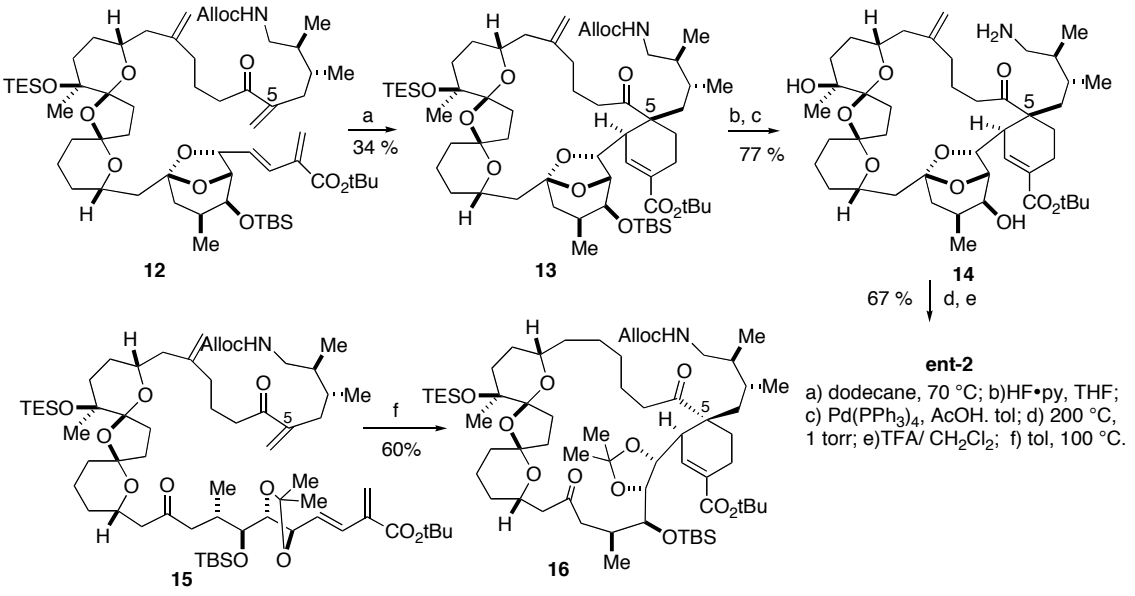



**Figure 3.3** Uemura biosynthesis proposal for Pinnatoxins

This strategy was put into practice by Kishi in his synthesis of ent-pinnatoxin A (Scheme 3.2). Compound **12** was heated in toluene to afford a mix of products. The desired product **13** is shown. Exo selectivity was high (83: 17), but little stereocontrol was noted at the $C_5$ stereocentre (53 : 47). Interestingly, changing the solvent from dodecane to toluene and increasing the temperature to 100 °C resulted in an erosion of exo selectivity (66: 34). Compound **13** could be deprotected to compound **14** in two steps. Cyclization occurred cleanly, at a temperature of 200 °C, followed by a cleavage of the *t*-Butyl ester to yield ent-pinnatoxin A.[8] As an illustration of the difficulty in predicting the course of these intramolecular Diels–Alder reactions, acetonide containing compound **15** underwent cycloaddition in good yield to give compound **16** as a single diastereomer. Unfortunately the acetonide proved impossible to remove at a later stage in the synthesis.

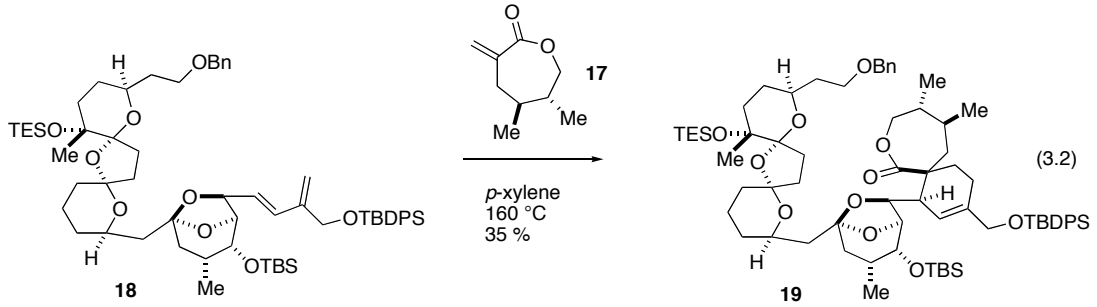
(8) The enantiomer was not biologically active in a mouse toxicity assay.

**Scheme 3.2**




**12** **13** **14** **15** **16**

An intramolecular Diels–Alder reaction of lactone **17** bearing an exo- methylene with diene **18** was reported by Hashimoto (Equation 3.2). This strategy also provided poor diastereoselectivity in the key Diels–Alder reaction, with a 45: 27 : 18 : 10 mixture of diastereomers. Desired Diels–Alder adduct **19** was isolated in 35 % yield.[9]




**18** **19**

The strategy most pertinent to our current one, involves the use of iminium dienophiles. Our efforts using iminium ion dienophiles will be summarized in the next section and are also the subject of much of this thesis.

(9) Nakamura, S.; Kikuchi, F.; Hashimoto, S. *Angew. Chem. Int. Ed.,* **2008**, *47*, 7091- 7094.

In 2000, MacMillan and coworkers described a series of organocatalytic reactions involving Diels–Alder reactions on iminium ions. These reactions were often highly enantioselective, but a variety of outcomes regarding endo/exo selectivity, illustrated in Figure 3.4, were noted.[10]

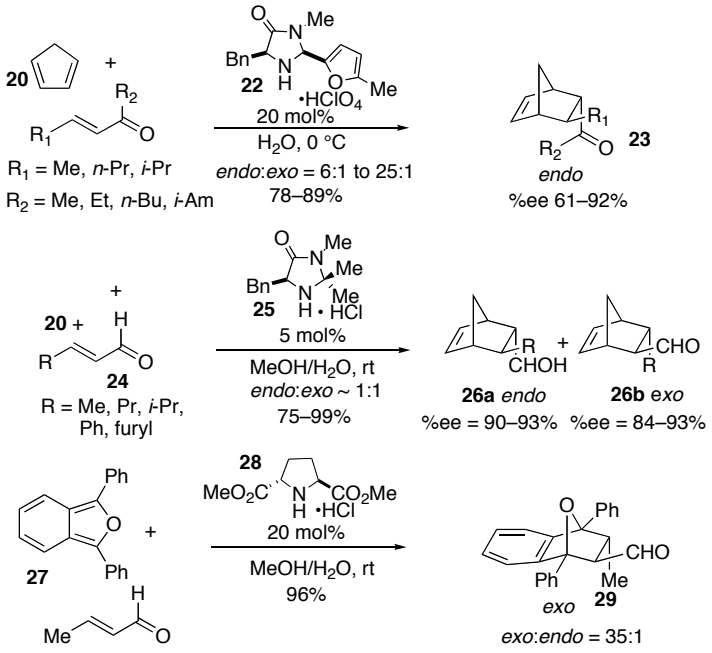



**Figure 3.4** Endo/exo selective reactions reported by MacMillan.[4]

A reaction between cyclopentadiene **20** and enones **21**, mediated by catalyst **22** gave Diels Alder adducts **23** with moderate to high endo selectivity. A similar reaction between **20** and various substituted acroleins **24**, mediated by catalyst **25** gave Diels–Alder adducts **26** with poor endo-exo selectivity. A reaction with isobenzofuran **27**, and crotonaldehyde, mediated by catalyst **28** gave Diels–Alder adduct **29** with high exo selectivity.

Since all of the spiro-imine natural products appear to result from an exo transition state involving an E diene, the exo selectivity observed in this last case deserves further

(10) a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243- 4244. b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458- 2460.

comment. A proposal was not made to explain the high exo selectivity of the last case, but I believe it may be specific to the isobenzofuran used (Figure 3.5). An interaction between one of the phenyls in the diene and the methyl ester of **28** is shown in endo transition state **30**, while this interaction would be diminished in transition state **31**. An alternate explanation is that there is a favourable cation π interaction between a phenyl group and the iminium cation in transition state **31**.


**Figure 3.5** possible explanations for the high exo selectivity with isobenzofuran **27**.

An important take-home message from these studies is that the iminium ions are more reactive than the corresponding ketones. This has implications for the Uemura biosynthetic proposal, since it may now be envisioned that compound **10** first undergoes iminium formation, to form compound **32** followed by a Diels–Alder reaction that would directly form pinnatoxin A (Figure 3.6).

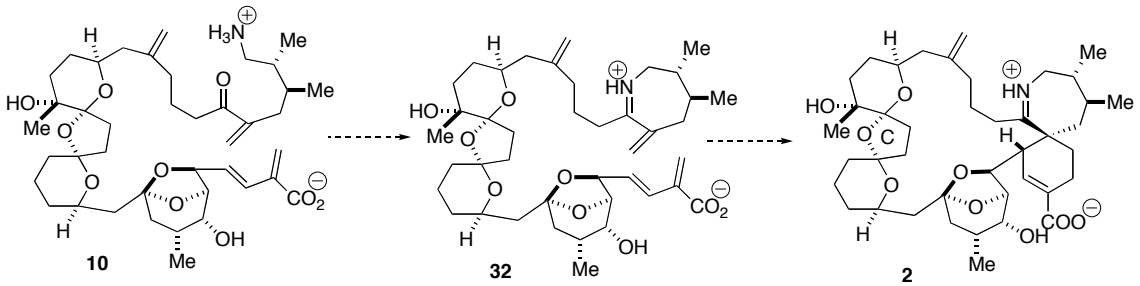


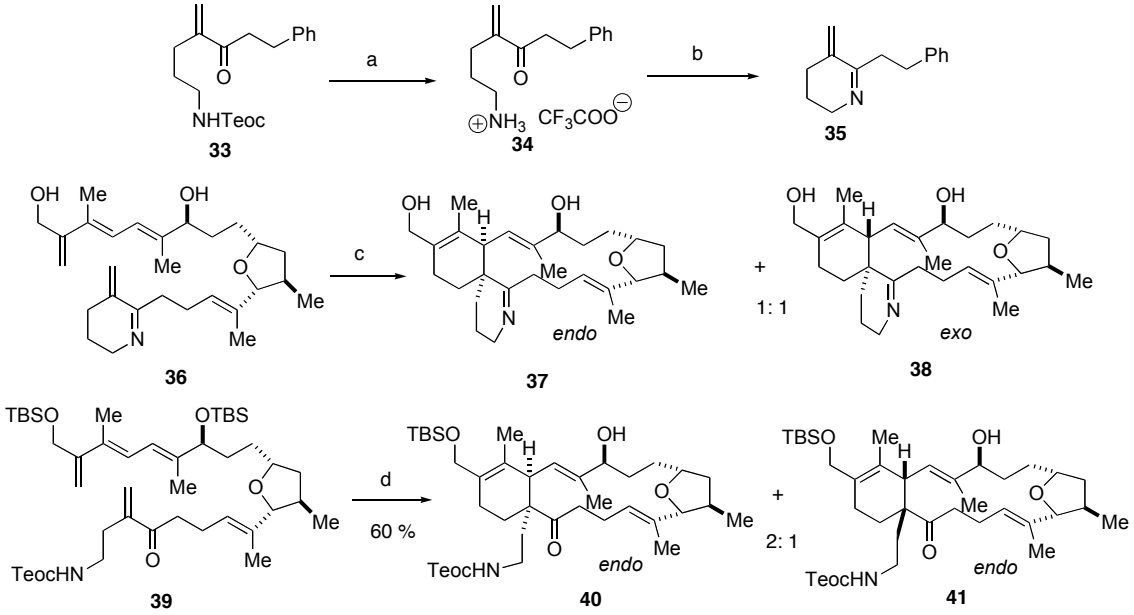

**Figure 3.6** Revised Uemura biosynthesis.

It is unclear what implications the formation of the cyclic iminium will have on facial selectivity. One hint is that computational studies from the Houk group suggest that

Diels–Alder reactions on iminium ions might be quite asynchronous.[11] Models of endo and exo transition states with cyclopentadiene and a dimethyliminium of crotonaldehyde suggest that the leading bond formed is approximately one angstrom closer than the lagging bond. This does have implications for the bond disconnections under discussion, since the leading bond is often further from stereocentres that impart diastereoselection in several of the examples discussed.[12]

Our group and the Kishi group concurrently pursued this strategy on different molecules. Kishi's efforts towards the total synthesis of gymnodimine were published in 2005 (Scheme 3.3).[13]

**Scheme 3.3**




a) TFA/ $CH_2Cl_2$; b) $NaH_2PO_{4(aq)}$; c) pH 6.5, $H_2O$, 36 °C; d) $C_6H_6$, BHT, 185 °C

(11) Gordillo, R.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543- 3553.

(12) Calculations of Diels–Alder reactions on the corresponding enals showed more synchronous transition states, with a leading-following bond difference that was often less than 0.5 angstroms.

(13) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997- 4000.

Model enone **33** underwent Teoc deprotection to give compound **34** followed by cyclization to form iminium **35** in phosphate buffer.[14] In a more elaborate system, iminium **36** was held in citrate buffer and a Diels–Alder reaction occurred with 1:1 endo/exo selectivity to give compound **37** and desired exo compound **38**. When the reaction was done thermally on intermediate **39**, only endo products **40** and **41** were observed. Product **41** arises from an attack on the undesired face of the enone. This is more evidence that changes in the structure of intramolecular Diels–Alder substrates can make dramatic changes to diastereoselectivity.

## III. Summary of Prior Approaches to Spiro-prorocentrimine in the Evans Group[15]

The purpose of this section is to summarize the prior approaches to spiro-prorocentrimine that were pursued in the Evans Group, with a strong emphasis on the findings and strategies that have most influenced the current route. It is hoped that this section will explain the context in which current decisions about the project were made.

Dr. Anna Chiu initiated the Spiro-prorocentrimine project in 2002 according to the following synthesis plan (Figure 3.7).[16]

(14) Inspection of their NMR spectra and comparison with our own exo methylene imines and iminiums revealed that the compound was protonated in the citric acid buffer.

(15) The work described in this section was carried out by Dr. Anna Chiu, Dr. Trixie Brandl, Dr. George Borg, Dr. Joseph Pero and Dr. Martin Juhl and individual parts are noted accordingly.

(16) Chiu, A. *PhD. Thesis*, Harvard University, **2005**.

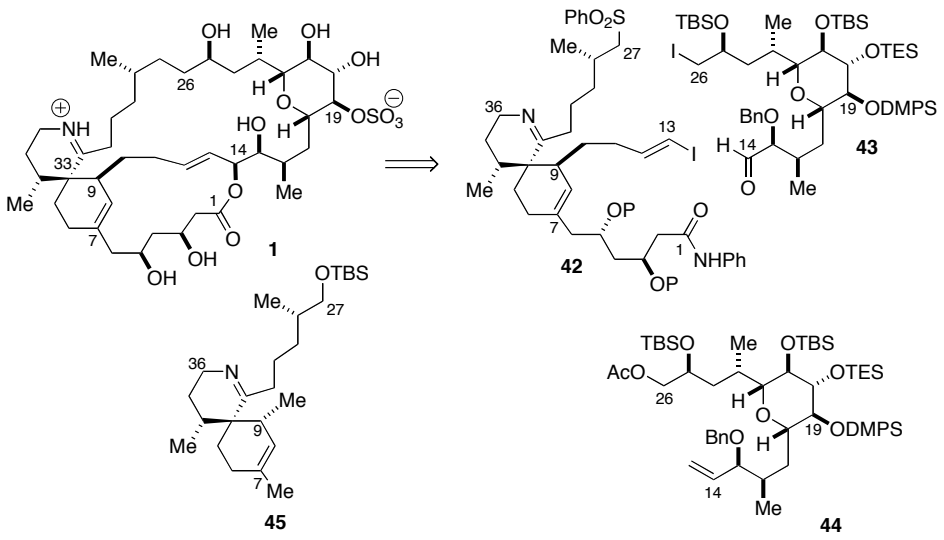
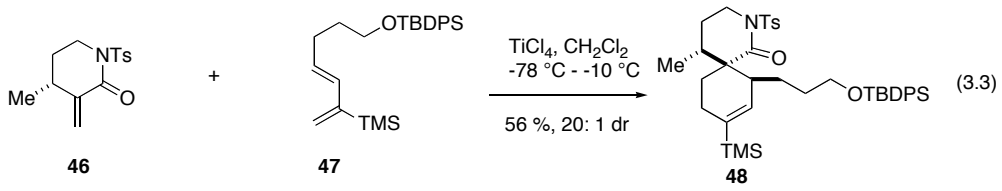



**Figure 3.7** Synthesis plan as envisioned by Dr. Chiu.[4]

Spiro-prorocentrimine was envisioned to arise from two fragments of roughly equal complexity. Spiro-imine synthon **42** would contain a sulfone at $C_{27}$, a vinyl halide at $C_{13}$ and an amide at $C_1$. Pyran synthon **43** would contain an iodide at $C_{26}$ alkyl, and an aldehyde at $C_{14}$. The $C_{26}$–$C_{27}$ bond construction would involve a sulfone alkylation followed by sulfone removal, the $C_{13}$–$C_{14}$ bond construction would involve an addition of a vinyl metal species into an aldehyde, and a macrolactonization between the alcohol formed at $C_{14}$ and the $C_1$ carboxylate would complete the spiro-prorocentrimine core. Significant progress was made towards all of the components, which can be found in Dr. Chiu's thesis. Pyran fragment **44** was constructed via a series of aldol reactions, and it was anticipated that the dimethylphenyl silyl group protecting the alcohol at $C_{19}$ would be orthogonal to the other silyl groups to allow selective sulfate installation.

Most pertinent to the future direction to the project were Dr. Chiu's efforts to construct the spirocyclic iminium core **45** of spiro-prorocentrimine.

An initial series of attempts were undertaken in collaboration with a postdoctoral fellow, Dr. Trixi Brandl. These involved the Diels–Alder reactions of exo-methylene lactams with *E*-dienes. A representative example is shown in Equation 3.3.




Tosyl-lactam **46** was allowed to react with diene **47** to afford Diels–Alder adduct **48** with high exo selectivity. A rationale for the exo selectivity is shown in structure **49** and **50**. An interaction with the back of the diene and the bound Lewis acid shown in endo structure **49** is presumably disfavoured.

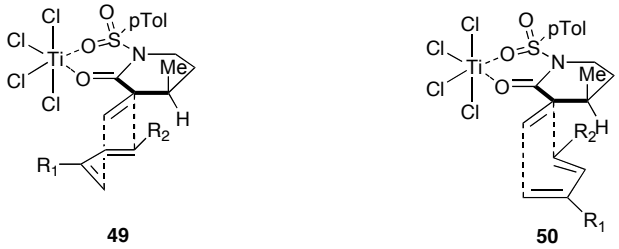
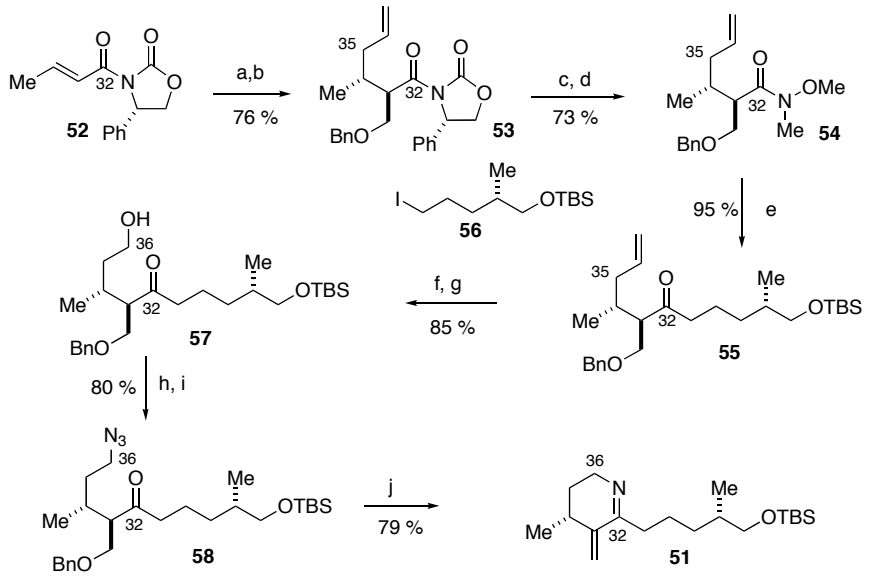



**Figure 3.8** Rationale for exo transition state in lactam Diels–Alder reaction.

Unfortunately, despite extensive experimentation, no conditions could be found that allowed the lactams to be converted to ketones, imines or iminiums. These included additions of alkyllithiums that were successful in the Romo case.[6]

Given the lack of success in elaborating the lactam to an imine or iminium, Dr Chiu decided to attempt a Diels- Alder reaction directly on cyclic iminium **51** bearing an exo-methylene group (Scheme 3.4).

**Scheme 3.4**

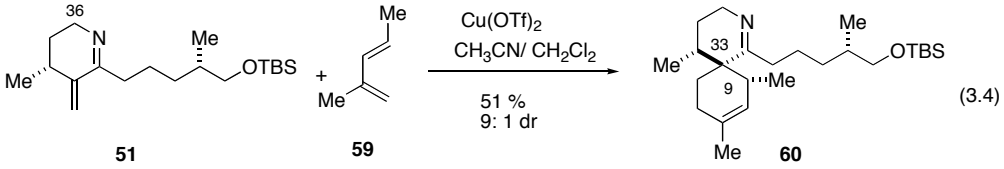



a) $Me_3SiCH_2CHCH_2$, $TiCl_4$, $CH_2Cl_2$, -78 °C; b) $TiCl_4$, *i*-$Pr_2NEt$, BOMCl, $CH_2Cl_2$, 0 °C to r.t.; c) LiOH, $H_2O_{2(aq)}$, THF/$H_2O$; d) MeNH(OMe), DCC, DMAP, $CH_2Cl_2$, 0°C; e) *t*-BuLi, **56**, then **54**, $Et_2O$, -78 °C; f) $O_3$, $CH_2Cl_2$/py, Sudan III, -78 °C, then DMS; g) $NaBH_4$, EtOH/ $CH_2Cl_2$, -78 °C; h) MsCl, py, 0 °C; i) $NaN_3$, DMF; j) $PPh_3$, $C_6D_6$, then MeOH/ $CH_2Cl_2$

A Sakurai allylation on imide **52** followed by alkylation with BOM chloride allowed the formation of compound **53** The oxazolidinone was replaced with a Weinreb amide, yielding compound **54**, which in turn was converted to ketone **55** via the addition of the alkyllithium derived from iodide **56**.[17] Ozonolysis of **55** followed by a selective reduction of aldehyde over ketone led to compound **57**, which was converted to azide **58** in a 2-step sequence. In practice the compound was stored at this stage. Exposure to triphenylphosphine resulted in azide reduction, aza-Wittig reaction, and benzyl alcohol elimination to form exo-methylene iminium **51**. This compound was both somewhat volatile and unstable, and was typically used with minimal purification.

(17) For the synthesis of **56** see, Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

Dr. Chiu found that imine **51** would react with model *E* diene **59** under the action of either Brønstead acid or metal triflate catalysis to give Diels–Alder adduct **60**. She identified copper II triflate as the optimal catalyst (Equation 3.4).




(3.4)

The diastereoselectivity was high, but unfortunately NMR studies revealed that the dominant product of the reactions is via an endo mode on the correct face of the iminium. While the correct facial attack results in the correct stereochemistry at $C_{33}$, the endo approach results in the incorrect stereochemistry at $C_9$. It became apparent that a different strategy was required to form the spiro-iminium core.[18]

In the end of her thesis, Dr. Chiu introduced the idea of constraining the dienes within macrocycles. Two optimistic possibilities would arise. One possibility would be that an *E* macrocycle would have a facial bias that would favour exposure of the face that would react in an exo fashion anti to the methyl group on the diene, shown in transition state **61**. The other possibility is that a macrocyclic *Z* diene would continue to react via an endo transition state, and constraining the *Z* diene within a macrocycle would place the *Z* diene in a reactive planar S-Cis conformation, shown in transition state **62**.

Conversely, there existed the risks that the favoured conformation of the dienes in the macrocycles would be a non-reactive S-trans conformation, that the E diene would continue to react via an endo transition state, or that the Z diene would prefer to react in an exo transition state due to additional steric interactions.

(18) Acyclic *Z* dienes were not reactive with the iminium ion under various conditions explored by Dr. Anna Chiu, Dr. George Borg, Dr. Pascal Bindschädler, and myself. Only very electron rich acyclic dienes, bearing silyloxy groups were found to react by Dr. David Marcoux. See the work in the following chapters for details.

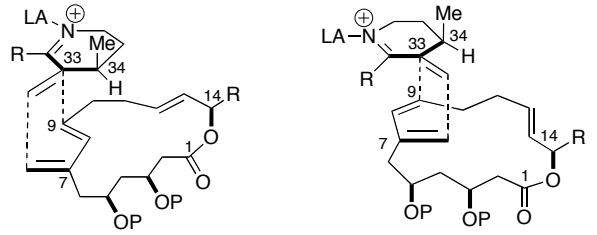
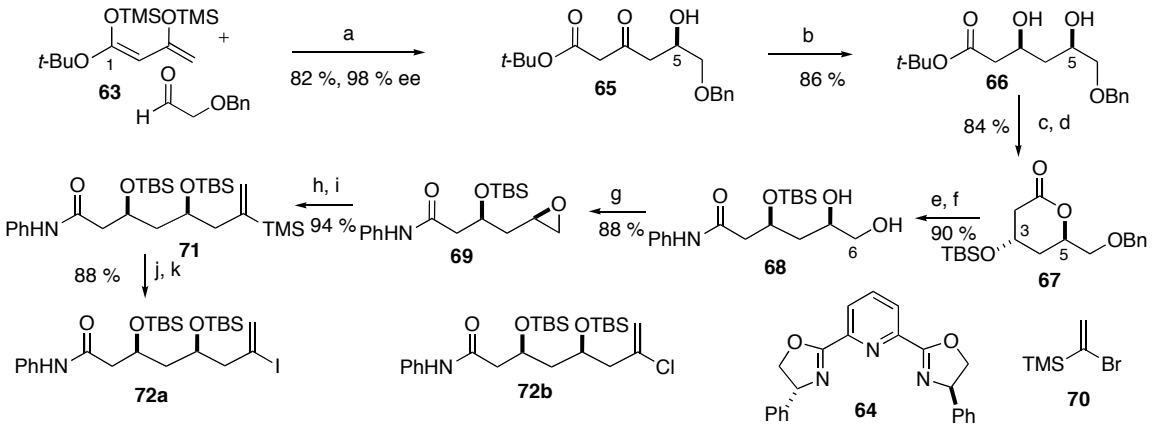



**Figure 3.9** Dr. Chiu's concept for macrocyclic dienes.

Dr. George Borg, Dr. Chiu's successor on the project, put the synthesis of both *Z* and *E* macrocycles into practice.[19] Dr. Borg employed two generations of approaches to the macrocycle, and only the second generation approach, which was carried out in tandem with Dr. Joseph Pero, a post-doctoral fellow, is discussed here.[20] The initial stages of the synthesis are described in detail in Scheme 3.4.

**Scheme 3.5**[21]




a) $Cu(OTf)_2$, **64**, $CH_2Cl_2$, -78 °C; b) $Et_2BOMe$, $NaBH_4$, THF, -78 °C; c) TFA, $CH_2Cl_2$, 0 °C; d) TBSCl, im, DMF; e) $PhNH_2$•HCl, $AlMe_3$, $CH_2Cl_2$/ tol, 0 °C; f) $H_2$, 10% Pd/C , EtOAc, HCl; g) NaH, TsIm, -20 °C; h) *t*- BuLi, then **70**, THF, -78 °C, then CuCN, warm to - 20 °C, then **69**, -78 °C, then - 50 °C, then -30 °C, then 0 °C; i) TBSOTf, 2,6- lutidine, $CH_2Cl_2$, -78 °C; j) ICl, $CH_2Cl_2$ , -90 °C; k) TBAF, THF, -78 °C.

(19) Borg, G. *PhD. Thesis*, Harvard University, **2007**.

(20) Pero, J. E. *Postdoctoral Report*, Harvard University, **2008**.

(21) The yields in this scheme were obtained by Dr. Pascal Bindschädler in the course of scale-up of this route.

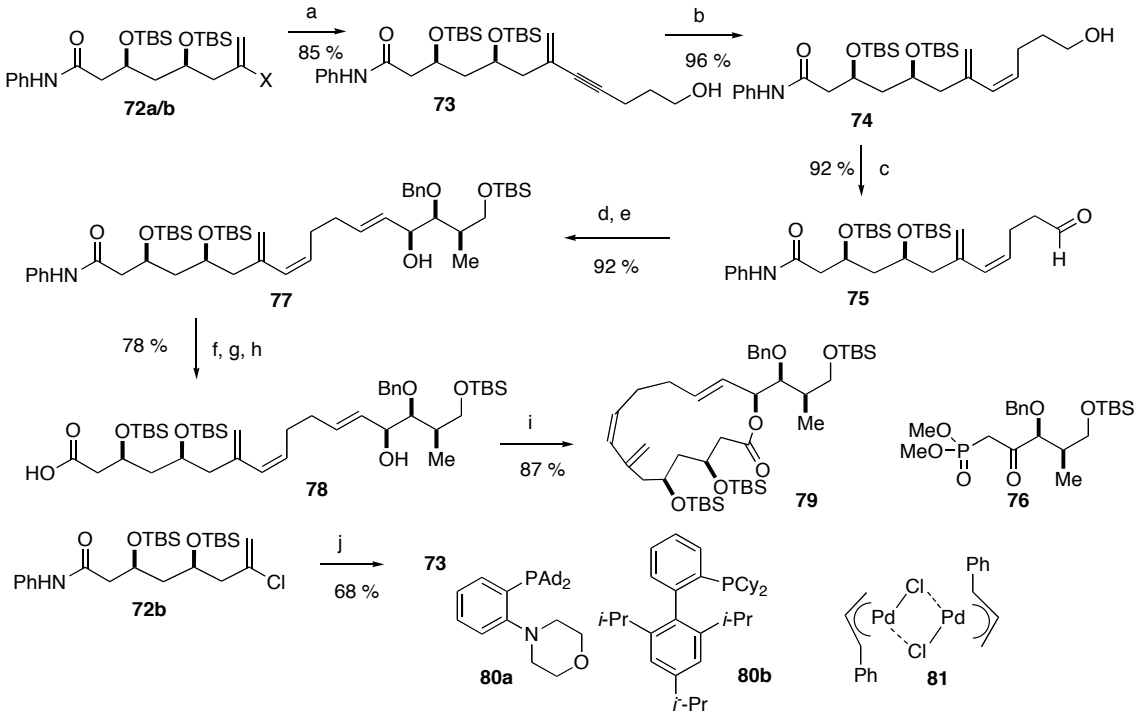
An aldol reaction between diene **63** and benzyloxyacetaldehyde, mediated by 5 mol % copper triflate complexed to ligand **64** set the stereocentre at $C_5$ in aldol adduct **65**. This stereochemistry was then relayed to $C_3$ by way of a Prasad reduction to give diol **66**. Differentiation of the alcohols at $C_3$ and $C_5$ was accomplished by cleavage of the $C_1$ ester and concomitant cyclization, followed by TBS protection of the $C_3$ alcohol to give lactone **67**, which was then opened with aniline. The benzyloxy group at $C_6$ was deprotected by hydrogenolysis to give diol **68**. Diol **68** was then transformed into epoxide **69** by selective tosylation of the $C_6$ alcohol in the presence of sodium hydride. Opening of the epoxide required extensive optimization, but ultimately reaction with an organocuprate derived from bromovinyltrimethylsilane **70** was effective. The alcohol at $C_5$ was protected to give vinyl iodide **71**. Treatment with iodine chloride and TBAF then gave vinyl iodide **72a,** which could not be separated, from approximately 10-15% of the corresponding chloride **72b**.[22]

Vinyl iodide **72a** represented the last common intermediate in the diene synthesis. Dr. Borg's synthesis of the *Z*-diene is shown in Scheme 3.6. A Sonogashira reaction with halides **72** and 4-pentynol provided ene-yne **73**. This was subject to reduction with Zn(Cu/Ag) to form *Z* diene alcohol **74** in high yield. Subsequent oxidation gave aldehyde **75**. HWE reaction with keto phosphonate **76** and a Felkin controlled Luche reduction gave allylic alcohol **77**.[23] A 3-step sequence then gave seco acid **78**. Cyclization under Yamaguchi conditions provided Z-diene **79**.

(22) Investigation of other iodonium sources such as $I_2$ or NIS gave inferior yields.

(23) A Mosher's ester analysis confirmed the product did not arise from chelate control. It was speculated the methanol in the reaction mixture precluded chelate formation.

**Scheme 3.6**




a) 4-pentyn-1-ol, $PdCl_2(PhCN)_2$, CuI, piperidine, 50 °C; b) Zn/Cu/Ag, MeOH/ $Et_2O$/ $H_2O$, 70 °C; c) $SO_3$•py, DMSO, *i*-PrNEt, $CH_2Cl_2$, 0 °C; d) **75, 76**, $Cs_2CO_3$, *i*-PrOH; e) $CeCl_3$•$7H_2O$, $NaBH_4$, MeOH/THF, 0 °C; f) TMSCl, im, $CH_2Cl_2$, then $Boc_2O$, DMAP, $CH_3CN$; g) $LiOH_{(aq)}$, $H_2O_{2(aq)}$, THF; h) MeOH/ NaOMe; i) **78**, 2,4,6-trichlorobenzoyl chlordie, $Et_3N$, thenDMAP, tol; j) 4-pentyn-1-ol, **80a**, **81**, $Cs_2CO_3$, THF, 66 °C

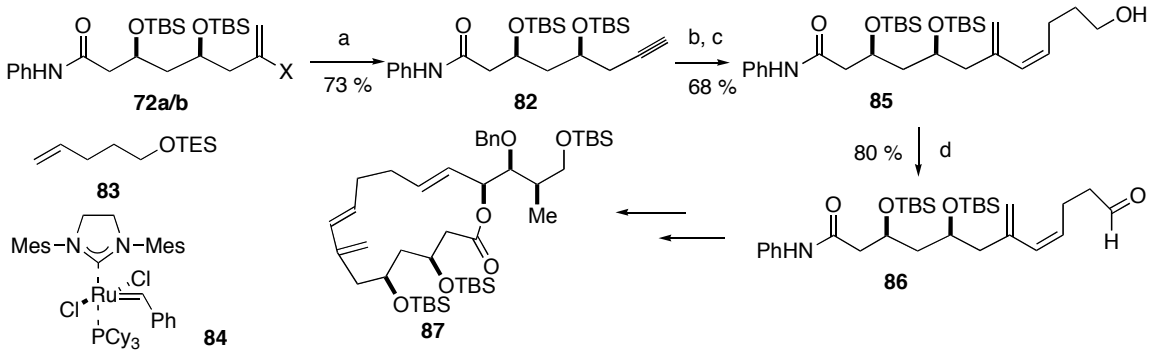
Chloride **72b** was not entirely consumed in the Sonogashira reaction. Over the course of several scale-up reactions conducted by Dr. Bindschädler we accrued several hundred milligrams of this compound. I investigated converting this compound to **73**. Use of Sonogashira conditions reported by Buchwald for aryl halides using X-Phos **80b** did not yield any product.[24] Fortunately, the use of Mor-Dal-Phos ligand **80a** with palladium source **81** gave an acceptable yield of **73**. This ligand was developed and employed by the Stradiotto group for a number of challenging aminations, however no previous disclosures of this ligand in Sonogashira chemistry have been made.[25] This may prove to be a useful system for challenging Sonogashira reactions in the future.

(24) Gelman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 5993- 5996.

(25) For the use of **80a** in the arylation of acetone with relatively unreactive aryl halides, see: Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194- 5194. I thank Dr. Kevin Hesp for suggesting the use of Dal Phos, and Dr. Rylan Lundgren for helpful advice.

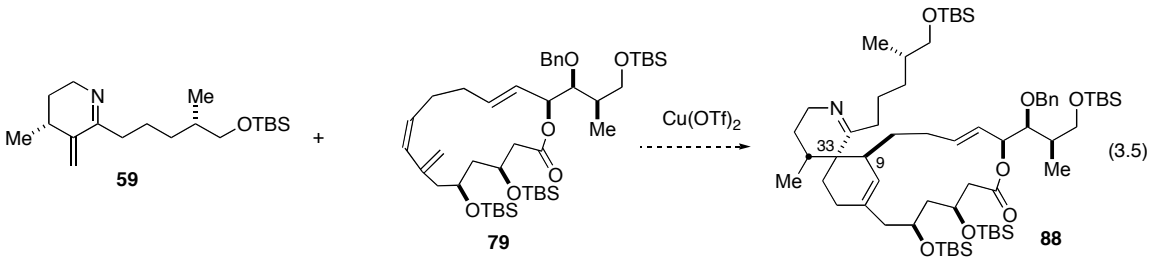
Dr. Borg had accessed *E* dienes with $C_3$-$C_5$ acetonide protection via an earlier route. The route developed by Dr. Joseph Pero is shown here (Scheme 3.7). Halides **72 are** exposed to LDA to give alkyne **82**, which is then subject to an ene-yne metathesis with alkene **83** using Grubbs catalyst **84**. Diene **85** was obtained in high yield after extensive optimization, the most important point being the use of argon as the atmosphere. Deprotection and oxidation gave aldehyde **86**, which was subject to a similar sequence to that of Scheme 3.6 to give *E* diene macrocycle **87**.

**Scheme 3.7**



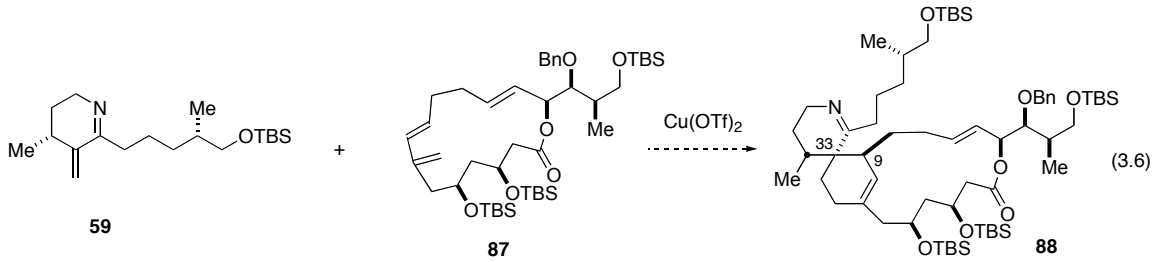

a) LDA, THF, -78 °C; b) **83**, **84**, tol; c) PPTS, MeOH/ $CH_2Cl_2$; d) $SO_3$•py, DMSO,*i*-PrNEt, $CH_2Cl_2$, 0°C.

With macrocycles **79** and **87** in hand, Dr. Borg attempted some preliminary studies of reactions between imine **59** and macrocycle **79** (Equation 3.5). Unfortunately no reaction or decomposition was observed with all conditions attempted, which involved a variety of Brønstead and Lewis acids. No product **88** or any stereoisomer thereof was obtained.




Also worrisome were observations by Dr. Pero that *E* diene macrocycle **87** was also

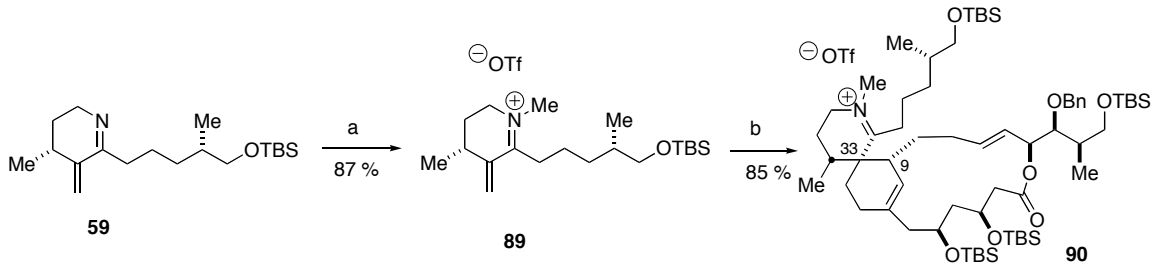
unreactive with imine **59** under the copper (II) triflate conditions developed by Dr. Chiu. No product **88** or any isomer thereof was observed (Equation 3.6).




(3.6)

Dr. Pero initiated a study on the feasibility of alkylating the iminium. The rationale behind this strategy was that the Pauling electronegativity of carbon is 2.5, while that of hydrogen is 2.1, and that of copper only 1.9. Dr. Pero was able to successfully alkylate **59** with methyl triflate to give iminium **89**. This did react with **87** to give a Diels–Alder adduct whose structure was believed to be **91** on the basis of 2D ROESY experiments done at the time (Scheme 3.8). It should be noted that I believe that the configurations at $C_{33}$ and $C_9$ were actually flipped. Evidence for this, and a rationale for this outcome is presented in chapter 6. I have drawn all of the Diels–Alder adducts as our understanding of the structure was at the time I started the project in this review section.

**Scheme 3.8**

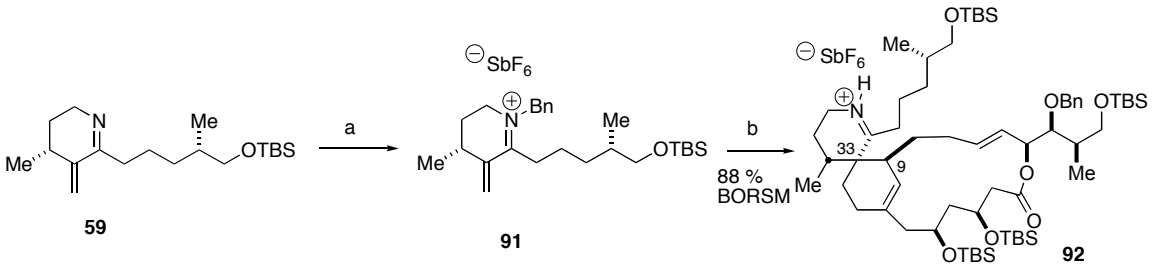



a) MeOTf, $Et_2O$, $CH_2Cl_2$, 0 °C; b) **87**, $CH_3CN$, 0 °C.

A different strategy was employed with *Z* macrocycle **79**. Dr. Pero exposed imine **59** to benzyl bromide and silver hexafluoroantimonate to produce what was believed to be iminium **91** on the basis of $^1$H NMR and mass spectral studies (Scheme 3.9). This then reacted with **79** to afford what was believed to be Diels–Alder adduct **82**. This reaction

did not proceed at ambient temperature and needed to be run at 40 ºC in DCE to obtain conversion. Additionally, there was no benzyl group on the iminium in the product. At the time this was attributed to solvolysis. My findings in chapters 5 and 6 showed that an alkylation did not occur in this reaction, and the configuration at $C_{33}$ in this molecule was flipped. Again, I have drawn these compounds as they were presented to me when I started this project.

**Scheme 3.9**

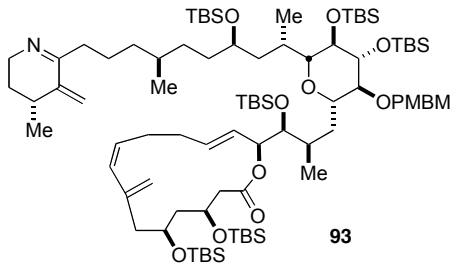



a) BnBr, $AgSbF_6$, $CH_2Cl_2$, 0 °C; b) **79**, DCE, 40 °C

With what appeared to be a solution to the Diels–Alder reactivity and stereochemical problems in hand, attention turned to the rest of the molecule. At this point, a large redesign was needed, as having the macrocycle in place before the Diels–Alder reaction was not compatible with the previous design. A new plan to target a Uemura type intramolecular Diels–Alder reaction was devised.

In this case, there were 3 variables that could be potentially modulated in an intramolecular Diels–Alder reaction. The first variable was if the dienophile reacted as an iminium or a enone. While an iminium would be more reactive, the enone would potentially present a less sterically demanding environment or have more degrees of freedom to participate in the desired cycloaddition. The second variable was if the diene needed to be in a *Z* or an *E* configuration to achieve reactivity or the proper stereochemistry. The third variable was if the 15 membered macrocycle would be present in the cycloaddition or would be formed after by macrolactonization. Since there were no

clues from nature about the order of the variables described above, the synthesis required enough flexibility to address the 8 scenarios arising from the above variables. Representative target molecules are **93** and **94**.



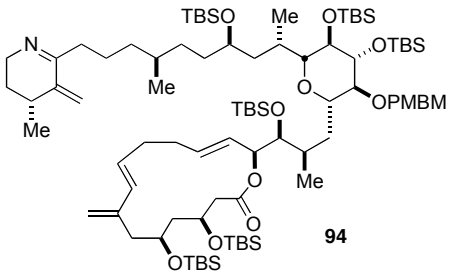
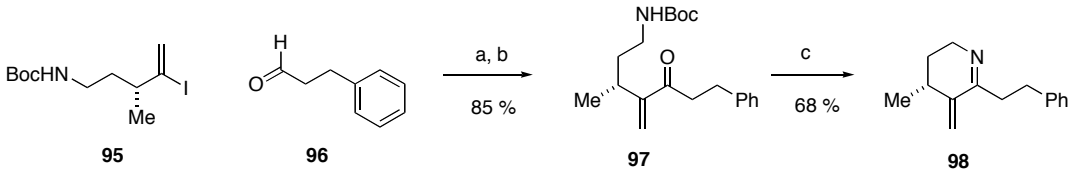




**Figure 3.10** Target for intramolecular Diels–Alder approach.

Dr Borg explored a mild method for the introduction of the imine at a late stage in the synthesis, which was analogous to the method used by Kishi. This involved the construction of iodoalkene **95**, followed by addition of **95** to aldehyde **96** in a NHK reaction. The resulting allylic alcohols were oxidized to enal **97**. The Boc group could be removed in an exceedingly mild manner, later found to compatible with both a *Z* diene and TBS groups by treatment with TES triflate, then TBAF that resulted in cyclization to iminium **98**.

**Scheme 3.10**




a) 0.5 % $NiCl_2$/ $CrCl_2$, DMF; $SO_3$•py, DMSO, *i*-PrNEt, $CH_2Cl_2$, 0 °C; c) TESOTf, 2,6-lutidine, $CH_2Cl_2$; then TBAF, THF, -78 °C

Dr. Borg explored elaborating pyran fragment **44**, available from Dr. Chiu's work, to an intramolecular Diels–Alder substrate. He made very significant progress in this area, which is described in his thesis. Ultimately it was decided that a route based on modifying **44**, which had been originally designed for a different sequence of

disconnects, would take too much effort to deliver sufficient quantities of material for proper investigation of intramolecular Diels–Alder reactions.[26]

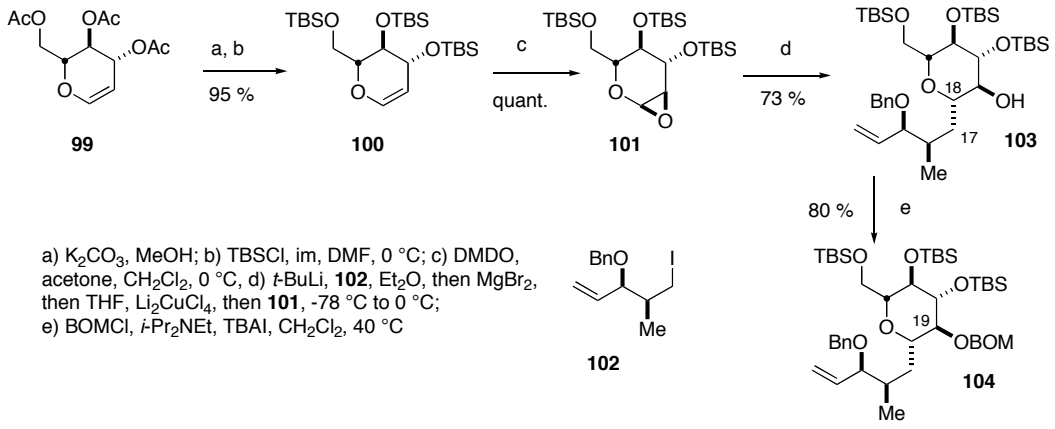
Dr. Borg initiated a new approach to an intramolecular Diels–Alder substrate, the majority of which was implemented by post-doctoral fellows Dr. Martin Juhl and Dr. Joseph Pero. A number of strategies were investigated, but only the one that was successful will be detailed here.

Dr Juhl and Dr. Borg investigated various approaches using tri-O-acetyl-D- glycal **99** as a starting material. This abundant compound contains 6 carbons and 3 stereocentres that map on to those of spiro-prorocentrimine and appropriate functional group handles for further elaboration. After extensive experimentation, Dr. Juhl developed precedent for a key transformation. This involved epoxidation of Tri- O TBS glycal **100** , followed by an anti- opening of the glycal epoxide **101** using a Grignard/ cuprate combination derived from iodide **102**. This allowed the formation of the $C_{17}$–$C_{18}$ bond, and set all of the stereocentres of the pyran ring on compound **103**. The diastereoselectivity of both the epoxidation and epoxide opening on this model system were high, and the sense of the induction is well precedented in the literature.[27] While silyl migration was somewhat problematic during efforts to protect this intermediate, Dr. Juhl found that BOM chloride enabled the protection of the $C_{19}$ alcohol on **103** to give compound **104** under conditions mild enough to preclude silyl migration.

(26) At this point in the synthesis, it was estimated that the longest linear sequence of the synthesis would be over 50 steps.

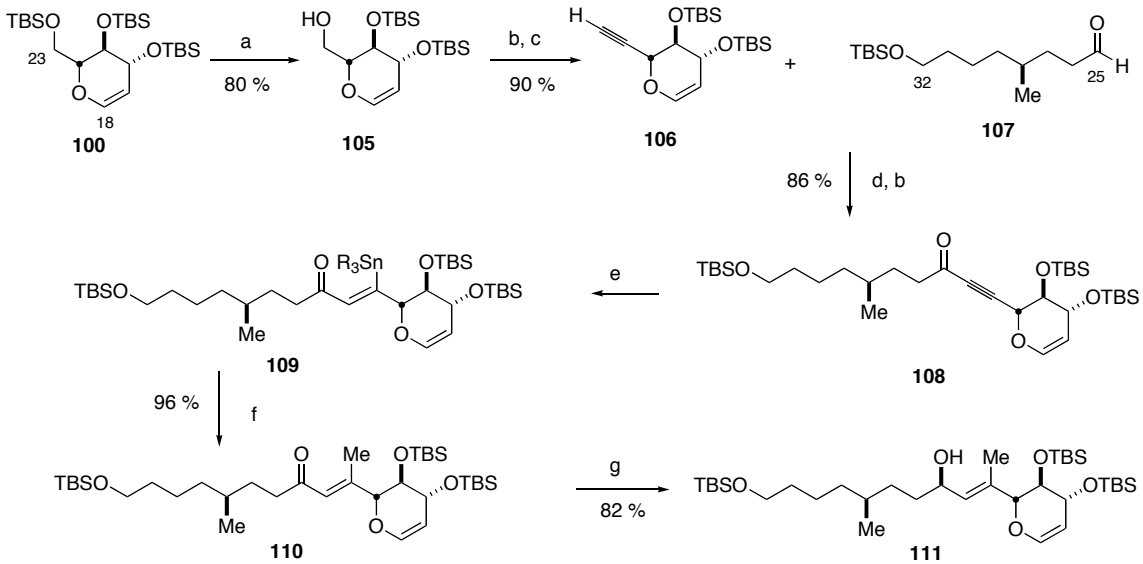
(27) Klein, L. L.; McWhorter, W. W.; Ko, S. S.; Pfaff, K.-P.; Kishi, Y. Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7362- 7364.

**Scheme 3.11**




A second important disconnection explored by Dr. Juhl involved setting the stereocentre at $C_{23}$ by an $A^{1,3}$ strain controlled hydrogenation, a strategy well known in our group.[28] The most convergent strategy would involve doing this hydrogenation before the epoxidation/ opening sequence. The synthesis of the hydrogenation substrate is described in scheme 3.12.

**Scheme 3.12**




a) HF•py, THF (2 recycles); b) $SO_3$•py, *i*-$Pr_2NEt$, DMSO, $CH_2Cl_2$, 0 °C; c) $CBr_4$, $PPh_3$, 2,6-lutidine, then LDA, THF, -78 °C; d) *n*-BuLi, **106**, then **107**, THF, -78 °C; e) $Bu_3SnH$, LDA, then CuCN, then **108**, THF, -78 °C; f) MeI, $Pd_2(dba)_3$, (*o*-tol)$_3$P, $K_2CO_3$, THF/NMP; g) (*S*)-CBS, HBCat, tol, -78 °C

(28) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866- 3868.

Compound **100** was subject to a selective deprotection to produce alcohol **105**.[29] This was oxidized and subject to a Corey-Fuchs reaction to produce alkyne **106**. The anion of **106** was added to aldehyde **107**, prepared from citronellol, giving an inconsequential mixture of diastereomers, which was oxidized to ynone **108**. Elaboration of the ynone to a trisubstituted olefin was challenging, but ultimately a 2-step procedure was employed. Addition of a stannyl anion gave stannane **109** with high *Z* –selectivity.[30] A Stille reaction then gave enoate **110**. A notably high loading of palladium needed to be used in this transformation. CBS/Itsuno reduction resulted in the synthesis of hydrogenation substrate **111**.

The envisioned hydrogenation is shown in Figure 3.11. $A^{1,3}$ strain was expected to give **112** in high diastereoselectivity.

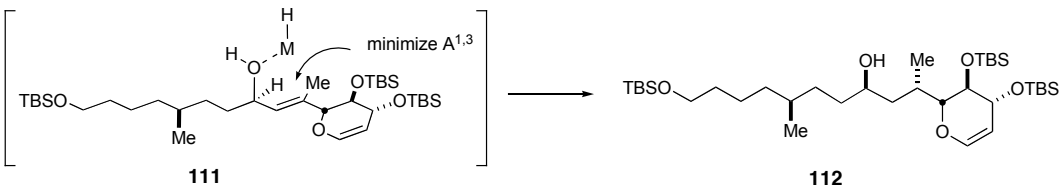



**Figure 3.11** Envisioned Hydrogenation

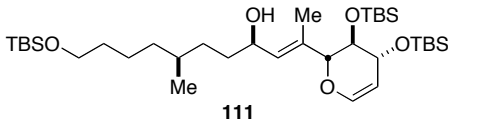
Unfortunately the hydrogenation of the allylic alcohol in the presence of the enol to produce compound **112** proved to be difficult (Table 3.1). The Brown catalyst (**113**) was not reactive, while chiral DuPhos based catalyst **114** gave poor olefin site selectivity. After extensive optimization, Dr. Juhl was able to obtain **112** in high yield using Crabtree's catalyst (**115**) in THF. He attributed the divergent reactivity compared with $CH_2Cl_2$ as a consequence of the attenuation of the Lewis acidity of **115** by THF. In general, rhodium catalyst **114** gave varying ratios of enol reduction product **116** or

(29) Anquetin, G.; Rawe, S. L.; McMahon, K.; Murphy, E. P.; Murphy, P. V. *Chem. Eur. J.* **2008**, *14*, 1592- 1600.

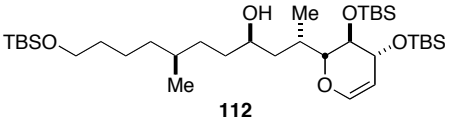
(30) Nielsen, T. E.; de Dios, M. A. C.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 7309-7313.

overreduction product **117** depending on the pressure employed. This transformation will be revisited extensively in chapter 4.

**Table 3.1** Selected Hydrogenation conditions explored by Dr. Juhl.



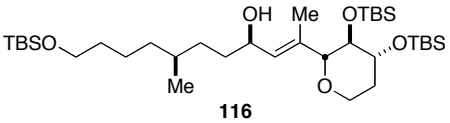

**111**



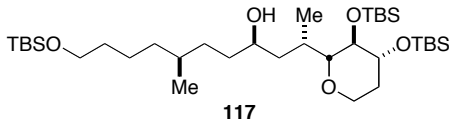

**112**

| entry | Catalyst | Pressure | Solvent | 112: 113 : 114 | % Conversion |
|---|---|---|---|---|---|
| 1 | **113**[a] | 600 psig | $CH_2Cl_2$ | 1:0:0 | 0 % |
| 2 | **114**[b] | 400 psig | $CH_2Cl_2$ | 4:1:4 | 40 % |
| 3 | **114**[b] | 900 psig | $CH_2Cl_2$ | 0:0:1 | 100 % |
| 4 | **115**[a] | 1 atm | $CH_2Cl_2$ | 1:0:2 | 100 % |
| 5 | **115**[a] | 1 atm | THF | 1:0:0 | 86 % |

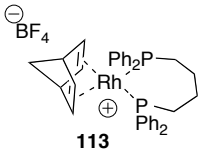
a) 10 mol %, b) 5 mol %



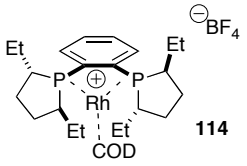

**116**



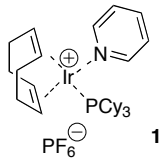

**117**




**113**



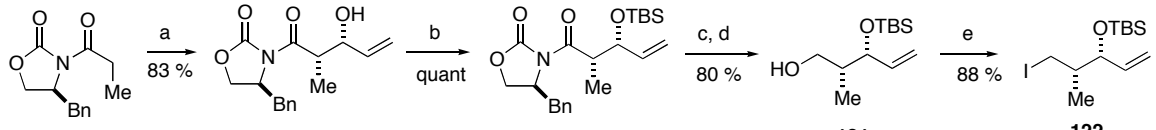

**114**




**115**

The synthesis continued with the fragment coupling. A protecting group modification was employed in the synthesis of the iodide used in the epoxide coupling (Scheme 3.13). An aldol reaction between oxazolidinone **118** and acrolein gives aldol adduct **119**. Compound **119** is silylated to give compound **120**. A 2 step reductive cleavage of the oxazolidinone gave alcohol **121**, which was then converted to iodide **122** in an Appel reaction. Dr. Joseph Pero prepared compound 122.

**Scheme 3.13**

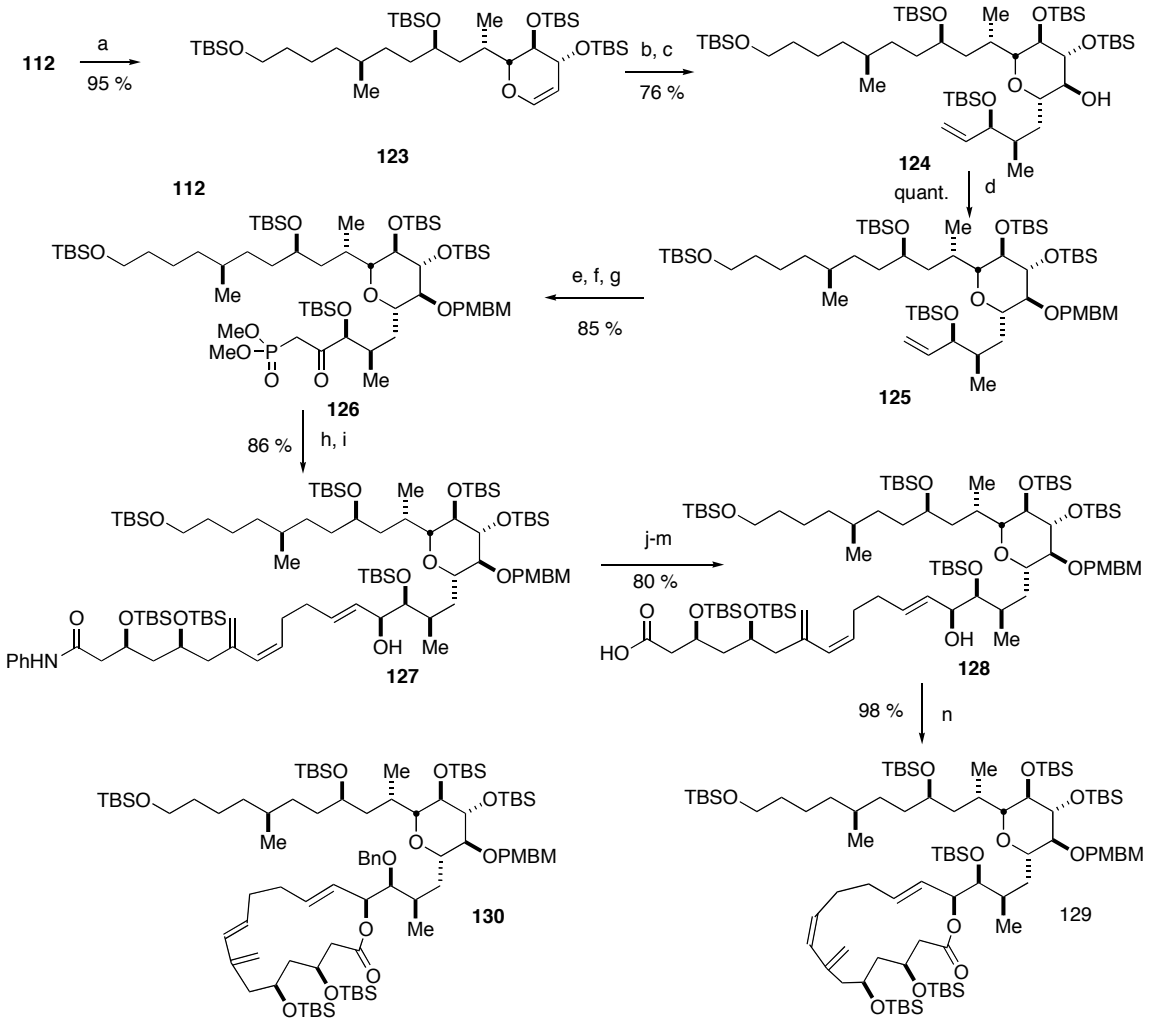



**118** **119** **120** **121** **122**

a) $Bu_2BOTf$, *i*-$Pr_2NEt$, acrolein, $CH_2Cl_2$, -78 °C- r.t; b) TBSCl, im, $CH_2Cl_2$; c) EtSH, *n*-BuLi, THF, -78 °C to 0 °C then **120**, -40 °C; d) $LiBH_4$, THF/MeOH, 0 °C- r. t.; e) $PPh_3$, $I_2$, im, THF/$CH_3CN$, r.t., then add **121**, 0 °C.

Compound **112** was silylated to afford compound **123**. (Scheme 3.14) Epoxidation of **123**, and opening with the organometallic derived from **122** afforded fragment-coupling product **124**. Protection of the $C_{19}$ alcohol afforded PMBM ether **125**. PMBM was chosen, as it was orthogonal to the silyl groups, and can be removed in the presence of isolated alkenes by oxidation. This would potentially allow selective sulfation at an appropriate time. Compound **125** was converted to β keto-phosphonate **126** in a three-step sequence of ozonolysis, lithiophosphonate addition and oxidation that was originally developed in work done by Dr. George Borg. At this point, either the *Z* or the *E* olefins may be introduced by HWE reaction with the appropriate aldehydes. Only the synthesis of the *Z* macrocycle will be shown here, but that of the *E* series was entirely analogous. HWE reaction with *Z* aldehyde **75** followed by a Luche reduction afforded allylic alcohol **127**, with the alcohol at $C_{14}$ formed in high diastereoselectivity. Hydrolysis of the N-Phenyl amide at $C_1$ was by a 4-step sequence. $C_{14}$ was transiently protected as a TMS ether, the amide was activated by adding a BOC group. Cleavage of the imide was followed by TMS cleavage to give seco acid **128**. This was cyclized under Shiina conditions to form macrocycle **129**. *E*- macrocycle **130** was formed by an analogous procedure.

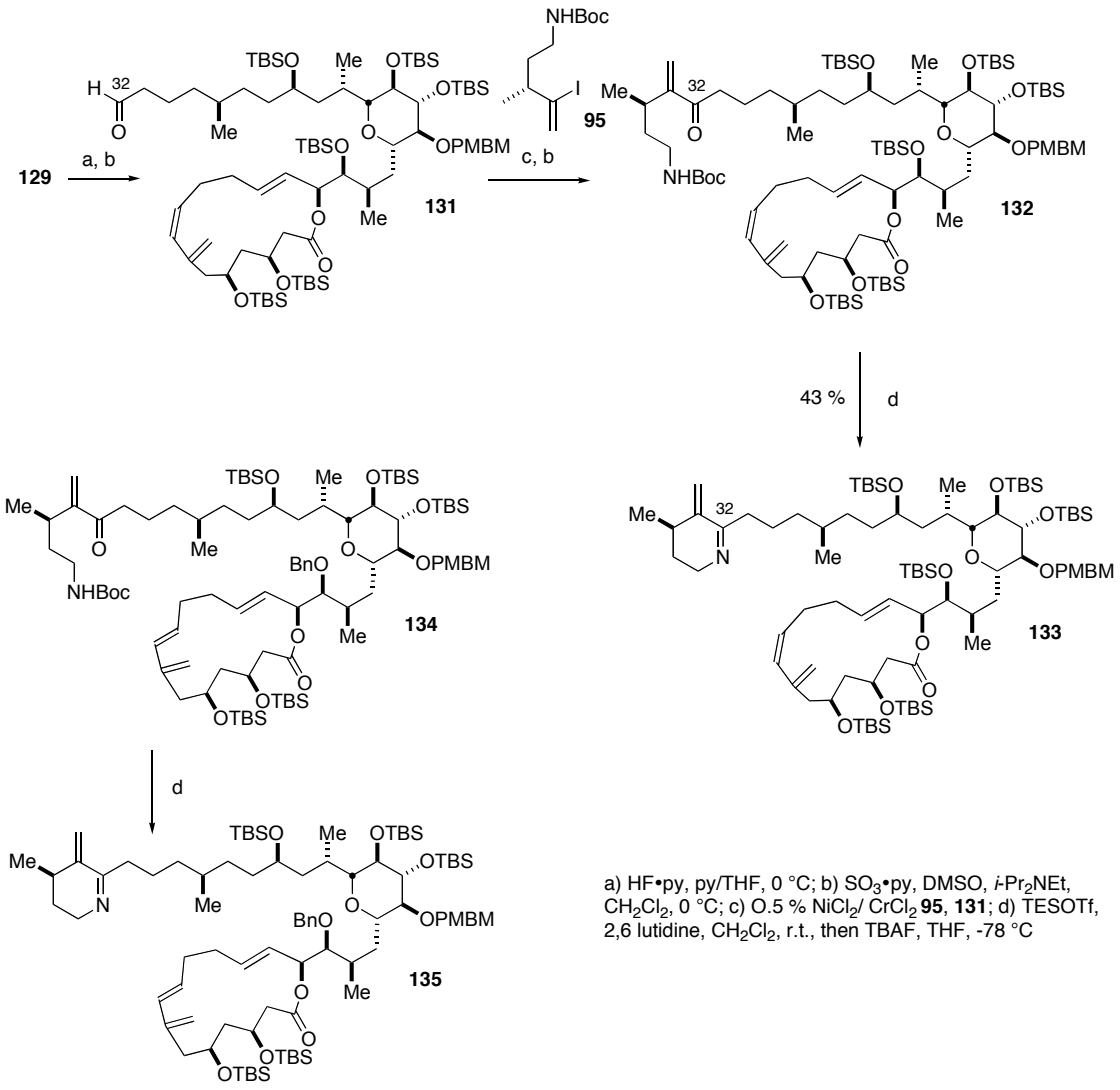
**Scheme 3.14**




a) TBSOTF, 2,6-lutidine, $CH_2Cl_2$, -78°C; b) DMDO, acetone, $CH_2Cl_2$, 0 °C; d) *t*-BuLi, **122**, $Et_2O$, -78 °C, then $MgBr_2$, then $Li_2Cl_4$, then epoxide, -78 °C- 0 °C; d) PMBMCl, *i*-$Pr_2NEt$, TBAI, $CH_2Cl_2$, 40 °C; e) $O_3$;then $PPh_3$, $CH_2Cl_2$, -78 °C; f) $(MeO)_2P(O)Me$, *n*-BuLi, then aldehyde, tol, -78 °C g) DMP, $CH_2Cl_2$; h) *n*-BuLi, **126**, then **75**, THF, 0 °C; i) $CeCl_3 \bullet 7H_2O$, $NaBH_4$, MeOH/$CH_2Cl_2$, 0 °C; j) TMSCl, im, $CH_2Cl_2$; k) $Boc_2O$, DMAP, $CH_3CN$; l) $LiOH_{(aq)}$, $H_2O_{2(aq)}$, THF, -5 °C; m) AcOH/MeOH; n) MNBA, DMAP, $CH_2Cl_2$.

Elaboration to nitrogen containing compounds was conducted by deprotection of the alcohol at $C_{32}$ followed by oxidation to aldehyde **131** and addition of iodide **95** (Scheme 3.15). Oxidation formed enone **132**. This could then be converted to imine **133**. The analogous reaction was carried out in the *E* series to form enone **134** and imine **135**.

**Scheme 3.15**




## Intramolecular Diels–Alder attempts

With imines **133** and **135** in hand, attempts were made by Dr. Pero to run intramolecular Diels–Alder reactions (Figure 3.12). Application of the BnBr/$AgSbF_6$ conditions to imine **132** resulted in no reaction at lower temperatures, and decomposition at higher temperatures. **132** could be protonated using TFA to form salt **136**, but no Diels–Alder

reaction to form **137** was observed at 40 ºC.[31] Decomposition was observed upon heating to 70 ºC. In an attempt to avoid decomposition, alkylation with MeOTf formed iminium **138**, but no cycloaddition to form **139** was observed.

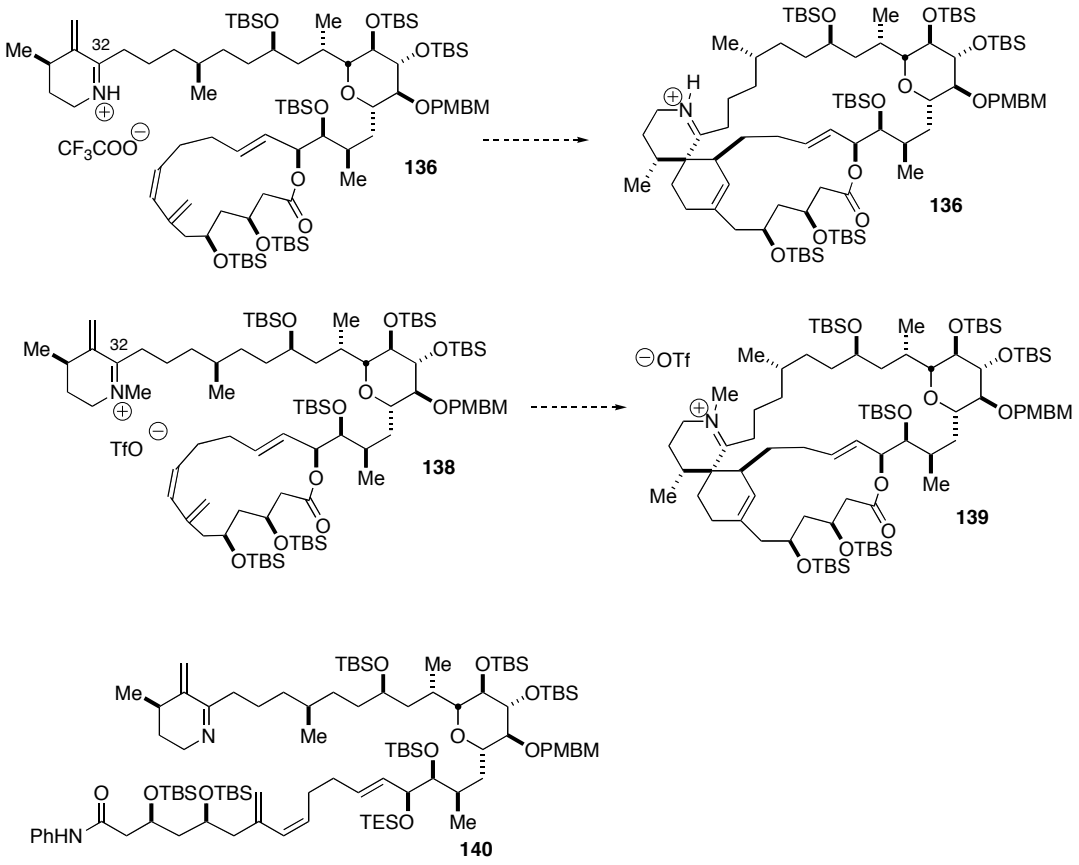



**Figure 3.12** Attempted intramolecular Diels–Alder reactions in the *Z* diene series.

Products attributed to isomerization of the *Z*- diene were observed upon heating. Acyclic compound **140** was prepared in anticipation that more degrees of freedom may be available to allow proper orbital overlap, but both protonation with TFA and methyl triflate failed to afford anything that Dr. Pero believed was a Diels–Alder adduct. A final

(31) In-light of the results obtained in chapter **5**, revisiting this result with non-coordinating counterions would have been desirable. Unfortunately the samples of **127** and **129** prepared by Dr. Pero had decomposed over several years of storage. I felt that the failure of **131** to react was enough evidence that it was not worth revisiting the entensive chemistry that would be needed to re-prepare compounds **127** and **129**.

series of attempt in the Z series was done by Dr. Martin Juhl, and involved conducting thermal reactions with enone **132**. Enone **132** did not undergo reaction, even upon heating to 110 ºC in toluene. Heating to 150 ºC caused decomposition. A Lewis acid catalyzed Diels–Alder reaction with $Me_2AlCl$ also failed because of extensive decomposition of the substrate.[32]

With these discouraging results from the *Z* diene series, attention turned to the *E* series. Only protonation was attempted for activation of compound **135**. Attempts were also made with acyclic *E* diene analogous to **140**. No Diels–Alder reaction was observed despite allowing the reaction to progress for 6 days.

Unfortunately no reaction was observed. Enone **134** did not react under thermal conditions at 110 ºC and decomposition was noted at 140 ºC.

At this point, Dr. Pero felt that the intramolecular Diels–Alder reaction was not viable with these substrates. The rationale was that they could not achieve conformations in which proper orbital overlap occurred to promote the Diels–Alder reaction. In the end of his post-doctoral report, Dr. Pero designed an intramolecular Diels–Alder route toward spiro-prorocentrimine.

## IV. Considerations for the Intramolecular Diels–Alder Synthesis Plan

Since a Diels–Alder reaction that produced compound **92** did work in an intermolecular fashion, Dr. Pero proposed the following synthesis plan (Figure 3.13). An intramolecular Diels–Alder reaction between imine **141** and *Z* diene **142** would afford Diels–Alder adduct **143**. This would then be subject to a ring closing metathesis reaction to form the

(32) Roush has shown IMDA reactions with *Z*-dienes employing this Lewis acid: i) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402- 7403. ii) Yakelis, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 957-960. In the course of later studies, I observed that $SnCl_4$ apparently does promote *inter*molecular Diels–Alder reactions between macrocyclic dienes and enones, but the enone component displayed poor facial selectivity.

$C_{26}$–$C_{27}$ bond in compound **144**. In the RCM route, removal of an orthogonal protecting group on $C_{25}$ would produce allylic alcohol **145**. It was hoped this alcohol could be employed to direct a reduction of the olefin at $C_{26}$–$C_{27}$.

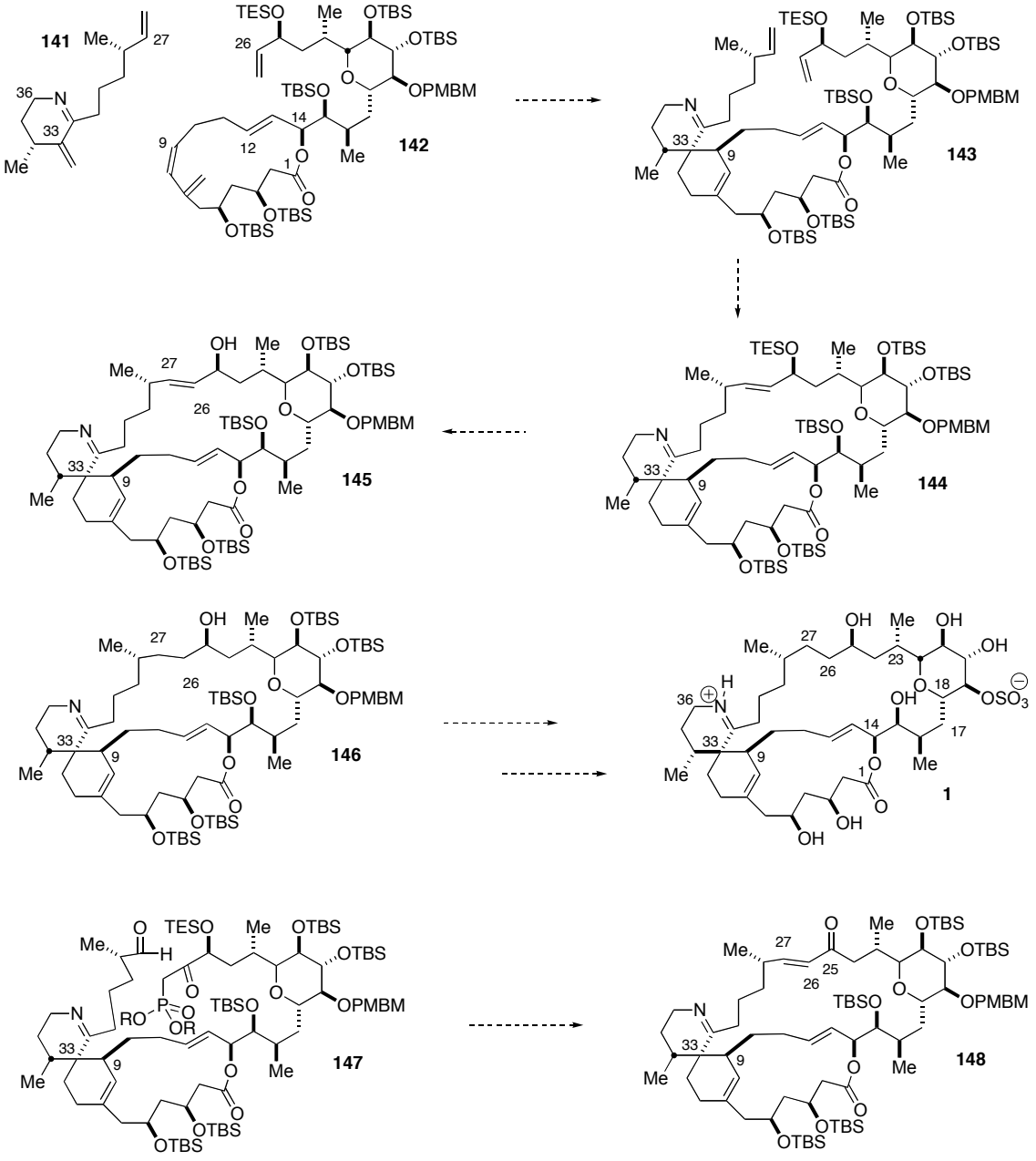



**Figure 3.13** Redesigned synthesis plan for spiro-prorocentrimine.

This was ambitious, since there are other olefins in the molecule, however hydrogenation of olefins bearing directing groups that spare olefins with no directing groups are known.[33]

In light of the results presented in Chapter 4, it is also worth considering that since the olefins in the molecule are in chiral environments, matching and mismatching of chiral catalysts may produce olefin selection even in the absence of directing group influences. Such interactions would be best determined empirically. If a successful reduction occurred, this would produce alcohol **146**. This would be only several protecting group manipulations away from spiro-prorocentrimine. Other strategies to form that bond, such as an HWE reaction could be envisioned, but the RCM is particularly attractive since it may be performed with an intact stereocentre at the $C_{25}$ position. An HWE reaction on a molecule such as **147** would result in a product with a ketone at the $C_{25}$ position, which would require a selective reduction on a macrocycle. My own experience with peloruside A (albeit a smaller, more crowded, and presumably less flexible molecule) suggested this might be a difficult proposition.

At this point I took over the project, and was tasked with implementing this strategy. In redesigning the synthesis for this strategy, I decided to keep the best attributes of the prior work, while taking the opportunity of the redesign of the synthesis to address several inefficiencies. These efforts are described in the next 3 chapters.

**Conclusion**

The efforts towards spiro-prorocentrimine by my predecessors on the project were summarized. Imine based Diels–Alder reactions were developed. The imine and iminium

(33) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375- 9376.

ion dienophiles were found to be poorly reactive with *Z* dienes and to give endo selective reactions with *E* dienes in intermolecular reactions. The synthesis of several macrocycles containing Z and *E* dienes was developed. These did undergo intermolecular Diels–Alder reactions with dienophiles. The work on spiro-prorocentrimine concluded with the synthesis of several substrates designed for intramolecular Diels–Alder reactions. None of these underwent Diels–Alder reactions, which was attributed to the molecule failing to achieve conformations that enabled proper overlap of the diene and the dienophile. An intermolecular Diels-Alder strategy was proposed to continue the synthesis of spiro-prorocentrimine.

# *Chapter 4*

## Synthesis of the Macrocyclic Diene[1]

### I. Preparation of the Hydrogenation Substrate

According to the synthesis plan presented in chapter 3, spiro-prorocentrimine **1** is envisioned to arise from a late stage Diels–Alder reaction between imine **2** and elaborate *Z*- macrocycle **3** (Figure 4.1) followed by a ring-closing metathesis and other functional group manipulations. The synthesis of **2** and Diels–Alder reaction studies will be the subject of chapter 5 and 6, while the synthesis of **3** is the subject of this chapter. Compound **3** in turn would be assembled from $C_1$–$C_{12}$ fragment **4**, available from the work of Dr. George Borg, and $C_{13}$–$C_{26}$ fragment **5**, generated from the glycal epoxide based coupling used by Dr. Martin Juhl in the preceding chapter. The substrates for the epoxide opening would be $C_{14}$–$C_{17}$ synthon **6** and $C_{18}$–$C_{26}$ synthon **7**.

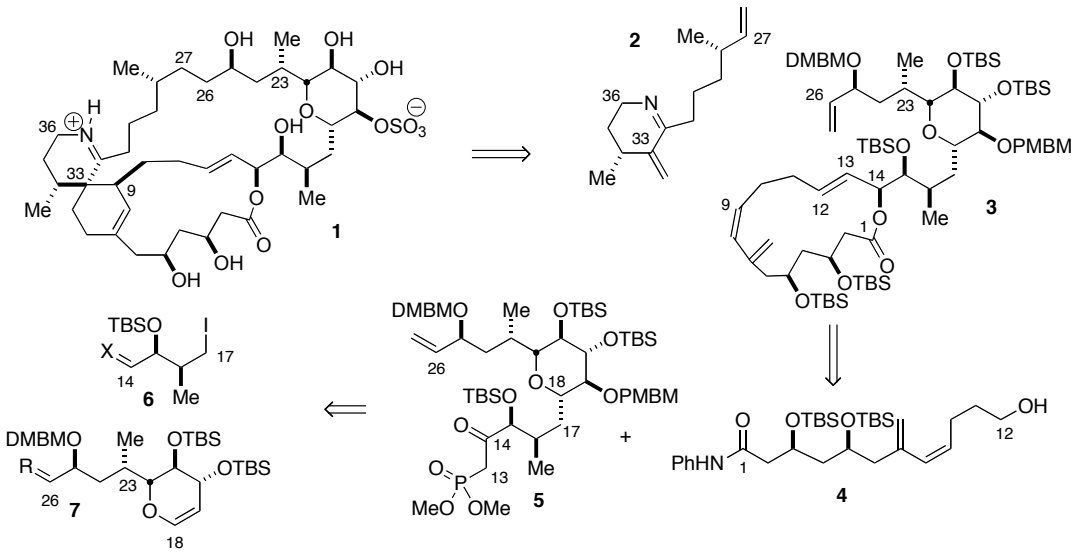



**Figure 4.1** Synthesis plan for spiro-prorocentrimine.

(1) Portions of the work described in this chapter were well precedented by the work conducted by Dr. Martin Juhl, Dr. Joseph Pero and Dr. George Borg that was described in Chapter 3. This is noted where applicable. Some of the work in this chapter was preformed with Dr. Pascal Bindschädler, and is noted where appropriate.

Initial efforts focused on the synthesis of the pyran section **7** of the molecule. After considering a variety of options, it was decided that keeping tri-*O*-acetyl-D-glucal **8** as the starting material presented the most efficient and precedented approach to this piece since **8** possesses the correct stereocentres at $C_{22}$–$C_{20}$, as well as handles for functionalization at $C_{23}$ and $C_{18}$ as shown in Figure 4.2.[2]

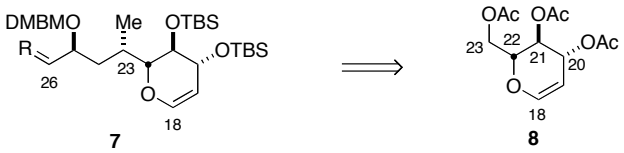
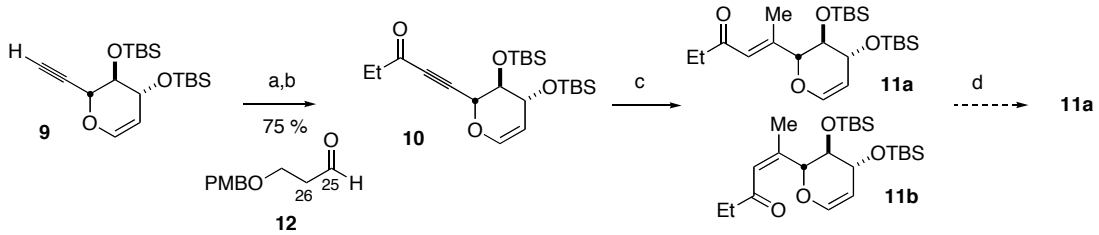



**Figure 4.2** D-Glycal as mapped on to fragment **7**.

An approach to a trisubstituted alkene was attempted on a model system. The anion derived from alkyne **9** was added to propionaldehyde and oxidized to ynone **10** (Scheme 4.1).

**Scheme 4.1**




a) *n*- BuLi, **9**, the EtCHO, THF -78 °C; b) *i*-$Pr_2NEt$, DMSO, $SO_3$•py, $CH_2Cl_2$; c) $Me_2CuLi$, $Et_2O$, -78 °C d) see text

Addition of methyl copper to ynone **10** resulted in decomposition, however addition of dimethyllithium cuprate led to a mixture of *Z* and *E* olefins **11a** and **11b**, despite a cryogenic quench.[3,4] This mixture was inseparable, and could not be equilibrated using either thiols or DMAP/ DMAP- HCl.[5,6] Had this approach worked, acrolein surrogate **12** would have been used instead of propionaldehyde.

(2) The price of Tri-O-Acetyl-D-glucal from VWR is $60.80 for 25 g (92 mmol). The amount of 75 g was sufficient for all of the work described herein.

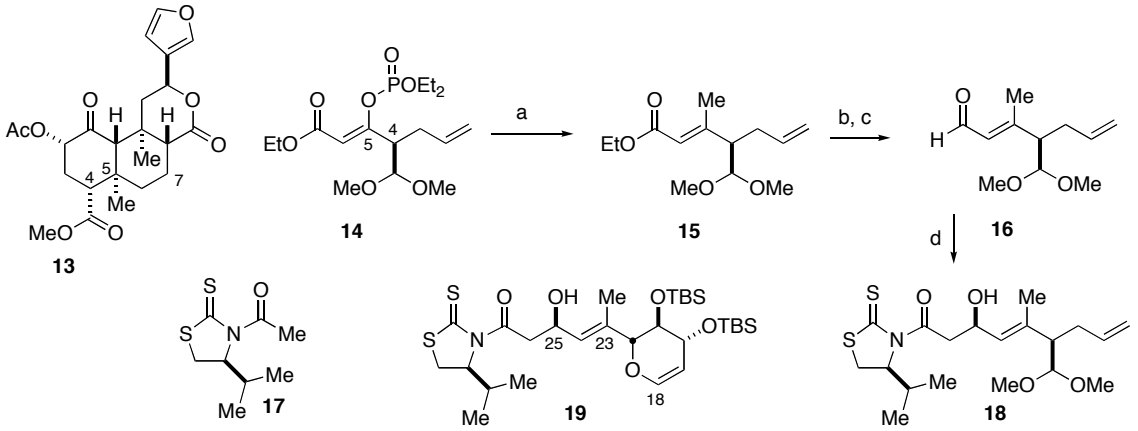
(3) Nilsson, K.; Andersson, T.; Ullenius, C; Gerold, A. Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051- 2058.

(4) In retrospect, $Et_2O$ was a poor choice of solvent. THF is known to favour the formation of *syn*-carbocupration products, which would have led to **10b** in this case, while $Et_2O$ is known to lead to scrambling by formation of allenoates. See reference 3 for details.

(5) Significant elimination of an OTBS group was observed upon treatment with 4-*t*-buthiophenol/DMAP.

With these discouraging initial results, it was decided in the interests of time to more closely follow the result of Dr. Juhl. However, the use of stoichiometric palladium and organostannanes at such an early stage in the synthesis required reexamination (Chapter 3 Scheme **3.12**). This was due to both aesthetic and practical reasons. Because of the price of precious metals at the time this transformation was under investigation (early 2009), ordering such a large quantity of palladium had become unattractive.[7] A similar stereoarray to the one desired was produced in the course of the Evans synthesis of salvinorin A **13**,[8] where an iron mediated coupling of methyl magnesium chloride with enol phosphate **14** gave rise to trisubstituted olefin **15** (Scheme 4.2)**.**[9]

**Scheme 4.2**




a) $Fe(acac)_3$, MeMgCl, THF, -20 °C; b) DiBAlH, $CH_2Cl_2$, -78 °C; c) $MnO_2$, $Et_2O$; d) **17**, *N*-Ethylpiperidine, $Sn(OTf)_2$, **16**, $CH_2Cl_2$

The α, β–unsaturated aldehyde **16**, derived from the product of cross coupling, proved to be an excellent substrate for a Nagao type acetate aldol with thiazolidinethione **17**, giving

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(6) For DMAP, see Keck, G. E.; Boden, E. P.; Mabury, S. A.; *J. Org. Chem.* **1985**, *50*, 710- 712.; For Thiols, see Aroyan, C. E.; Miller, S. J.; *J. Am. Chem. Soc.* **2007**, *129*, 256- 257.

(7) The estimated cost was over $5 000 for the amount of palladium dba projected to be required contrasted with Juhl's purchase of approximately the same amount for $1000 2 years prior.

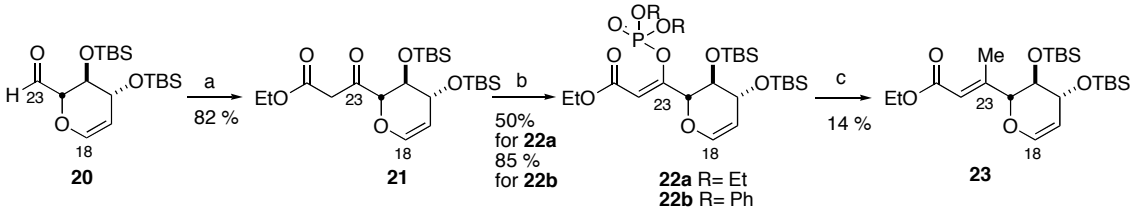
(8) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968-8969.

(9) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199-1205.

stereoarray **18**.[10] This maps well on the corresponding $C_{18}$–$C_{26}$ target fragment for spiro-prorocentrimine **19**, so such a strategy was implemented for the construction of **19**.

Aldehyde **20**[11] was subjected to a Roskamp reaction with ethyl diazoacetate, mediated by niobium pentachloride, forming $C_{23}$–$C_{24}$ bond in β-ketoester **21**.[12] Based on anecdotal evidence from the group, the Roskamp reaction was quite sluggish, which was attributed to the sterically demanding environment around the aldehyde.[13] No products resulting from competing chemistry at the enol ether were observed (Scheme 4.3).

**Scheme 4.3**




a) $NbCl_5$, $N_2$=CHCOOEt, b) LiHMDS, ClP=O(OPh)$_2$ or ClP=O(OEt)$_2$, THF c) MeMgCl, Fe(acac)$_3$, NMP, THF, -25 °C or $Me_2CuLi$, $Et_2O$, -78 °C to -40 °C

The β-ketoester could readily be transformed into enol phosphates **22a** or **22b**. Unfortunately, neither compound was a competent partner for cross coupling with a methyl organometallic, either mediated by iron, or using lithium dimethylcuprate.[14]

In the lithium dimethylcuprate coupling, trace quantities of the desired trisubstituted enoate **23** could be obtained. The predominant product recovered in attempts at these transformations was β-ketoester **21**. It was presumed that the nucleophillic attack is

(10) Nagao, Y.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391-2393.

(11) (a) Anquetin, G.; Rawe, S. L.; McMahon, K.; Murphy, E. P.; Murphy, P. V. *Chem. Eur. J.* **2008**, *14*, 1592- 1600. (b) Tius, M. A.; Hagadone, M. R. U. S. Patent 5,292,899, **1994.**

(12) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258- 3260. For the use of niobium pentachloride in this transformation, which is cleaner than $SnCl_2$, see: Yadav, J. S.; Subba Reddy, B. V.; Eeshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005***, 61*, 875- 878.

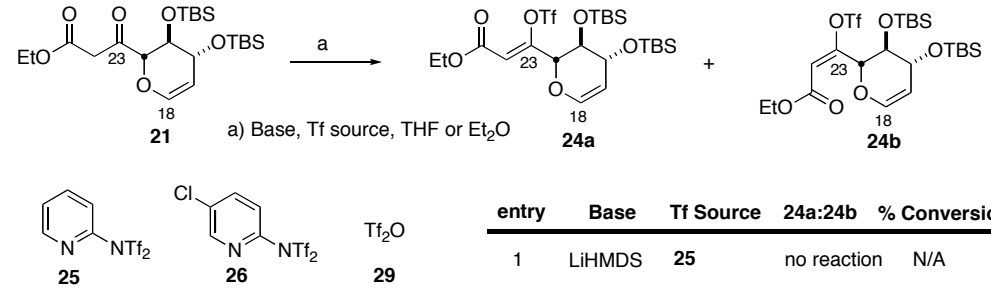
(13) Dr. Drew Adams ran a Roskamp reaction on a less hindered aldehyde at ambient temperature for a shorter time. See: Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048- 1049.

(14) Sum, F. W.; Weiler, L. *Can. J. Chem*. **1979**, *57*, 1431- 1441.

occurring at the phosphorus centre, rather than the desired carbon, releasing the β-ketoester. This can be attributed to the sterically crowded environment around $C_{23}$.

Attention switched to the use of an enol triflate in the cross coupling, as reported by Fürstner.[15] Unfortunately, use of the lithium enolate of the β-ketoester to form *Z*-enol triflate **24a** was unsuccessful using the conditions of Fürstner (phenyl triflamide **25**, LiHMDS deprotonation, DMPU as co solvent) (entry 1, Table 4.1). Use of the more reactive Comins reagent **26** was also unsuccessful (Entry 2). [16]

**Table 4.1**




| entry | Base | Tf Source | 24a:24b | % Conversion |
|---|---|---|---|---|
| 1 | LiHMDS | **25** | no reaction | N/A |
| 2 | LiHMDS | **26** | no reaction | N/A |
| 3 | NaHMDS | **26** | 6: 1 | 30 % |
| 4 | KHMDS | **25** | 1:1 | 50 % |
| 5 | LiHMDS | **29** | **24a** only | 50 % |
| 6 | NaHMDS | **29** | **24a** only | 40 % |
| 7 | NaH | **29** | **24a** only | quant. |

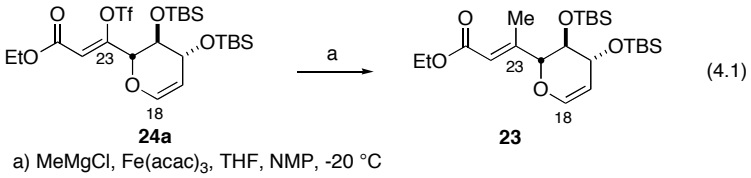
Upon switching to more reactive sodium and potassium enolates, formed using the respective hexamethyldisilazides, better reactivity with **25** and **26** was obtained, at the expense of olefin geometry (Entry 3, 4).[17] It is assumed that a greater amount of the non chelated *E*-enolate **27** relative to *Z*-enolate **28** is formed with the larger sodium and

(15) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem*. **2004**, *69*, 3943- 3949.

(16) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **33**, *42*, 6299- 6302.

(17) As assessed by $^{19}F$ NMR of the enol triflates in the crude reaction mixture.

potassium cations.[18] Additionally, the more reactive *E*-enolate **27** could be triflated faster, in a Curtin–Hammett type scenario. Since only one geometric isomer of the enol phosphates had been observed using LiHMDS enolization, it was decided to return to lithium bases and employ the more reactive triflating agent triflic anhydride **29**. Exposure of **21** to LiHMDS, followed by triflic anhydride, resulted in the formation of a 50% yield of the desired enol triflate as solely the *Z* isomer (Entry 5, table 4.1). The balance of the material was β-ketoester **21**. Now that a route was secured to the enol triflate, an iron mediated cross coupling was attempted, which proceeded cleanly to afford enoate **23** (equation 4.1).




(4.1)

After validating this method of formation of the enoate, attention returned to optimization of the triflate formation. Since the near quantitative formation of enol phosphate **22b** with LiHMDS as a base showed that enolization was complete, it was anticipated that the partial triflation was due to a competitive decomposition of the triflic anhydride.[19] An obvious candidate was hexamethyldisilazane, the conjugate acid of LiHMDS. Evidence supporting this was mixing of triflic anhydride and hexamethyldisilazane in $CDCl_3$, albeit at room temperature, in an NMR tube, which resulted in instantaneous reaction. Accordingly, a base with a conjugate acid unreactive with triflic anhydride, sodium hydride, was used for the enolization (entry 7, Table 4.1). Almost complete conversion to the enol triflate at -78 °C was observed. An added bonus was that the enol triflate was detected as only one geometric isomer. This contrasts to the triflation results found with

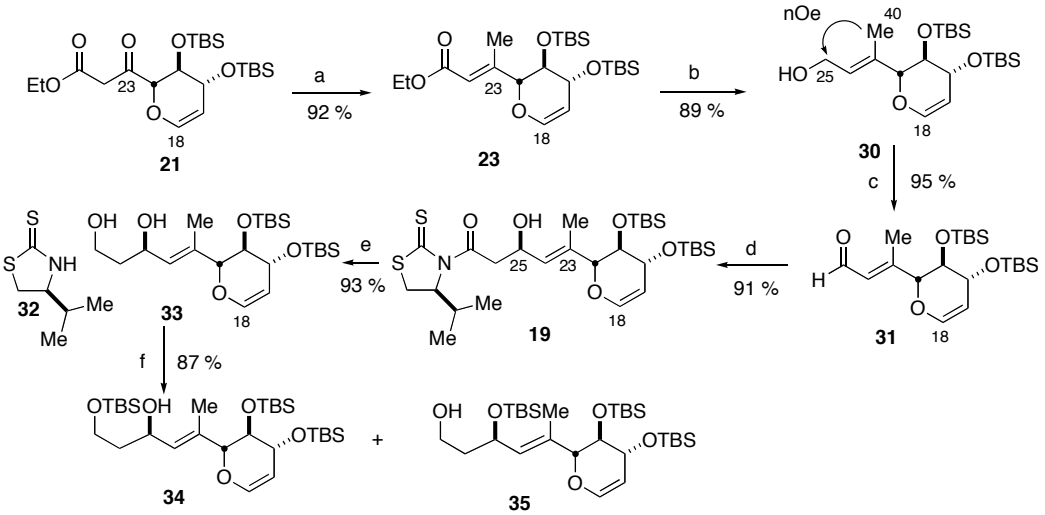
(18) An area for future investigation would be the addition of 18-crown-6 to selectively favour the *E*-enolate. This may permit a geometrically controlled synthesis of trisubstituted olefins from a common precursor.

(19) In retrospect, the low yield for the formation of **22a** may be attributed to a similar decomposition route.

sodium hexamethyldisilazide and the less reactive triflating agent **26** (entry 3). A reasonable explanation is the kinetic quench scenario, where the population of the undesired but more reactive *E* sodium enolate is actually very low, and the activation barrier for quench of the *Z* sodium enolate with the powerful triflating reagent triflic anhydride is less than the barrier for interconversion of the enolate isomers. An alternate explanation is that no mechanism for the interconversion of the enolate isomers exists in the absence of the proton source hexamethyldisilazane.

In practice, the enol triflate formation and cross coupling were conducted in one pot.[20] The enoate was readily reduced to the allylic alcohol **30** using DiBAlH (Scheme 4.4). Hydroalumination of the enol ether was not a competing reaction at -78 °C, but when the reduction was run at higher temperatures, some decomposition was noted that could be attributed to this side reaction. Observation of a nOe enhancement between the protons at the $C_{40}$ methyl and $C_{25}$ allylic position indicated the desired *E* olefin geometry.

**Scheme 4.4**




a) NaH, rt, then -78 °C, add **29**, then warm to - 20 °C, add $Fe(acac)_3$, MeMgCl; b) DiBAlH, $CH_2Cl_2$, -78 °C; c) DMSO, *i*-$Pr_2NEt$, $SO_3$•py, $CH_2Cl_2$; d) **17**, *N*-Ethylpiperidine, $Sn(OTf)_2$, **31**, - 50 °C, $CH_2Cl_2$; e) $LiBH_4$, THF/ $H_2O$, 0 °C, f) TBSCl, $Et_3N$, DMAP, $CH_2Cl_2$

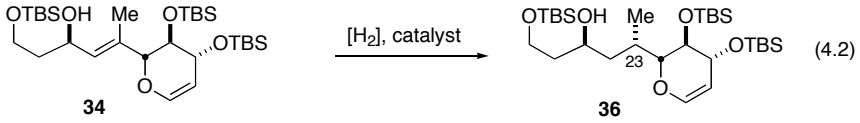
(20) While the enol triflate was stable to chromatography, higher yields were obtained in the one pot procedure.

A half reduction directly to aldehyde **31** was attempted, but was unsuccessful despite slow addition of DiBAlH solution or attempts to run the reaction in a thawing mixture of dichloromethane and toluene (approx -95 °C). Use of Red-Al® or lithium borohydride to reduce enoate **23** to allylic alcohol **30** were also unsuccessful.

The allylic alcohol could be oxidized to enal **31** using manganese dioxide, but Parikh–Doering conditions were more convenient on large scale.[21] Careful chromatography of enal **31** was required to remove materials such as DMS and DMSO, which could potentially serve as ligands, eroding the selectivity of the subsequent Nagao acetate aldol. The acetate aldol reaction was uneventful, providing **19** with 20 to 1 diastereoselectivity. Commercial stannous triflate (Strem) proved inferior to stannous triflate prepared according to a modified procedure of Dr. Ann Weber.[22] Auxiliary **32** was removed reductively, and the primary alcohol **33** was selectively protected. The reductive removal was unremarkable, however the balance of the material from the selective protection to form **34** was protection of the secondary alcohol to yield **35**.

## II. Hydrogenation Studies

The next challenge revolved around hydrogenation of the trisubstituted olefin in the presence of the enol ether to set the stereochemistry at $C_{23}$ in desired product **36** (equation 4.2).

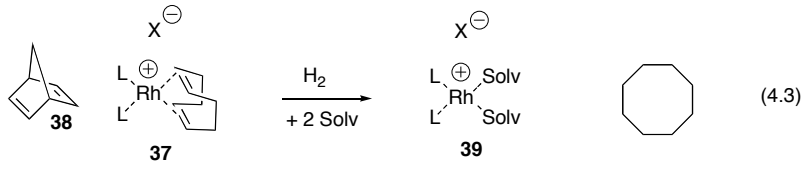


(4.2)

(21) Parikh, J. R.; Doering, W. v. E. **1967**, *89*, 5505- 5507.

(22) The ratio of $SnCl_2$ to triflic acid may be increased to 5 times that in the following publication: Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761. Fine grinding of the $SnCl_2$ is essential to ensure complete conversion in the consequently more viscous reaction. Dr. Paulo Vital developed this modification.

This reaction was not initially projected to be problematic, given that Juhl had found robust conditions for the selective hydrogenation of a trisubstituted olefin in the presence of an enol ether in a very closely related system (Chapter 3, Table 3.1). Technical considerations for the success of this reaction mainly revolve around the difficulty of monitoring high pressure hydrogenations while in progress. The small quantities of substrate (often 10 – 50 mg) employed in test runs,[23] combined with the relatively large volume of even the smallest hydrogenation bombs precludes accurately measuring pressure changes as an indicator of the progress of hydrogenation. Obtaining aliquots for chromatographic or spectral analysis is infeasible without specialized equipment, as depressurizing and opening the hydrogenation bomb would cause exposure to atmosphere, spoiling the catalyst. It should be noted most hydrogenation catalysts such as **37** are supplied as pre-catalysts containing a chelating diolefin such as cyclooctadiene or norbornadiene **38** which is hydrogenated off before productive hydrogenation can begin (equation 4.3).[24]




(4.3)

The solvate complexes such as **39** that are formed after removal of norbornadiene or COD are generally far more sensitive to water and oxygen than the initial precatalysts. An ideal procedure is therefore one that reliably hydrogenates the trisubstituted olefin in a predictable amount of time, with minimal hydrogenation of the enol ether. Furthermore,

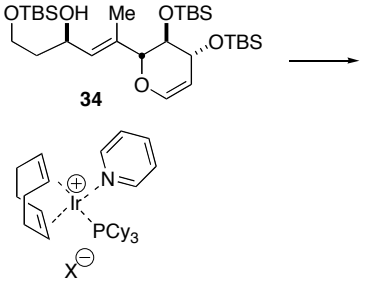
(23) While 10-50 mg of an intermediate 11 steps in is generally a very large quantity to use in scouting runs, the sensitive nature of the catalysts, coupled with the potential for over reduction if artificially high loadings of catalysts are used necessitate the use of relatively large quantities of substrate. Fortunately the efficiency of the synthesis of **35** allowed multigram quantities to be prepared.

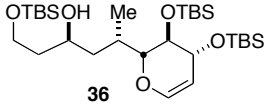
(24) The time for the initiation can often be slower than the complete hydrogenation of substrate. Differences between norbornadiene precatalysts (generally activated faster) and COD precatalysts can be pronounced. For a kinetic study comparing initiation rates of COD with norbornadiene rhodium complexes of bidentate phosphines, see: Heller, D.; Borns, S.; Baumann, W.; Selke, R. *Chem. Ber.* **1996**, *129*, 85- 89.

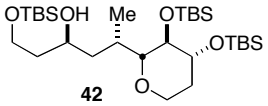
this procedure must be amenable to scale-up, from the original scale of the test- run to procedures on a gram or more of material to allow reasonable material throughput. The Juhl procedure offered such a solution, with the use of Crabtree's catalyst **40** in THF, conducted under a balloon of hydrogen. This reaction was ultimately conducted in a multigram scale in the course of Juhl's scale-up.

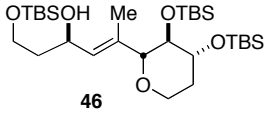
With the hydrogenation substrate in hand, the Juhl conditions for hydrogenation were attempted (Table 4.2, entry 1). Unfortunately extensive screening of a variety of loadings of Crabtree's catalyst in THF met with little success, as conversions were never higher than 50%, and conversion fell when the reaction scale was raised above 50 mg (entry 2).

**Table 4.2** Attempts to hydrogenate substrate **34**.[25]



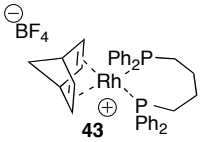



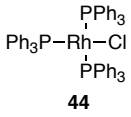




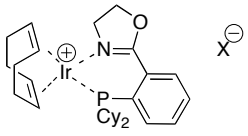
**40** X= $PF_6$
**41** X= tetrakis(3,5-trifluorophenyl)borate




**43**




**44**




**45** X= tetrakis(3,5-trifluorophenylborate)

| entry | Catalyst[a] | Pressure | Solvent | 36: 42 : 46 | % Conversion |
|---|---|---|---|---|---|
| 1 | **40** | 1atm | THF | 1:0:0 | 15 % |
| 2 | **40** | 200 psig | THF | 1:0:0 | 15 - 50 %[b] |
| 3 | **40** | 500 psig | THF | 2:1:0 | 35 % |
| 4 | **40** | 1 atm | $CH_2Cl_2$ | 0:1:0 | 100 % |
| 5 | **41** | 120 psig | THF | 1:0:0 | 40 %[c] |
| 6 | **41** | 100 psig | $Et_2O$ | 0:1:0 | 100 % |
| 7 | **43** | 200 psig | $CH_2Cl_2$ | 1:1:0 | 20 % |
| 8 | **44** | 200 psig | $C_6H_6$ | N/A | 0 % |
| 9 | **45** | 800 psig | $CH_2Cl_2$ | 0:0:1 | 10 % |

a) 5- 10 mol% **catalyst**, [**cat**] < 0.004 M
b) 50 % conversion was on 10 mg **34**, 15 % conversion was on 190 mg **34**
c) This yield was not reproducible

(25) Approximately 90 attempts were made to hydrogenate **34** before reliable conditions were developed The variation of pressure, solvent and catalyst identity was done in a manner that attempted to be systematic, and the results selected here represent various established boundary conditions.

Over reduction to **42** was observed with increased pressure, despite incomplete conversion of starting material (entry 3). Over the course of several of these runs, approximately 100 mg of the hydrogenation product was obtained, and NMR spectroscopy verified that it was being produced as one diastereomer. Use of Crabtree's catalyst in dichloromethane as the solvent resulted in complete hydrogenation, in accordance with the observations of Juhl, and one diastereomer, assumed to be **42**, was obtained (entry 4). Some of the Juhl hydrogenation substrate was available, and I was able to reproduce his procedure with his substrate, showing that the issue lay with my substrate rather than the batch of the catalyst or my technique.

A slight improvement was noted in some runs with the use of Crabtree's catalyst with a BArF ion **41** rather than hexafluorophosphate.[26] However, use of catalyst **41** proved very capricious, in that scale up to a moderate scale resulted in reduced and non-reproducible yields (entry 5). Unlike **40**, **41** is soluble in diethyl ether, so this solvent was attempted in anticipation that the attenuation of reactivity would be less than in the stronger coordinating THF. Unfortunately complete conversion to **42** was noted (entry 6).[27]

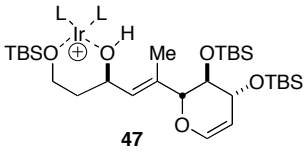
Attention switched to a wider range of catalysts. Unfortunately neither the Brown cationic rhodium catalyst **43** nor Wilkinson's catalyst **44** proved reactive at lower pressures (200 psig) (entries 7 and 8).[28] These catalysts were tested on both the alcohols

(26) Wüstenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174- 178.

(27) The lack of reproducibility and scalability in these hydrogenation reactions was attributed to physical properties related to hydrogen transport. Scaling a reaction up results in an increase in the volume to surface area ratio of the reaction, until larger size glassware is used. The depth of the reaction, and consequent size of the vortex created by stirring are possibly also factors, and vortex character is impossible to monitor in the non-transparent bomb. A mechanism for scale- related decline in yield might involve decomposition pathways through hydride-poor iridium species, which would increase in concentration if the reaction were starved of hydrogen.

(28) For the use of **43** in directed hydrogenations of allylic alcohols, see a) Brown, J. M.; Naik, R G. *J. Chem. Soc., Chem. Commun.* **1982**, 348- 352. b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866- 3868.

and the sodium alkoxides.[29] Some over hydrogenated product was noted in both cases. Complex **45**, bearing an achiral PHOX ligand was prepared, but appeared to hydrogenate only the enol ether leading to product **46**.[26] It is believed that the divergence in reactivity compared to the Juhl case is because of the presence of the potentially coordinating OTBS group at $C_{26'}$. While coordination to silyl groups is not typically invoked, the very electrophillic nature of the iridium catalyst, combined with the formation of a 6 membered ring **47** could make chelation favourable (Figure 4.3).



**47**

Figure **4.3** Proposed iridium chelate.

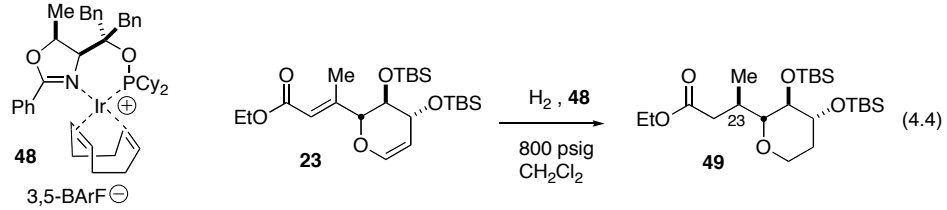
This chelate could suppress catalyst turnover, while leaving the catalyst open to non-productive decomposition.[30] A TIPS group at $C_{26'}$ was tried, but this appeared to suppress activity in hydrogenation altogether.

At this point, it was decided to attempt the hydrogenation at an earlier stage of the synthesis, on either enoate **23** or allylic alcohol **30**. In **34**, direction from the secondary alcohol at $C_{25}$ introduces the possibility of forming chelate **47** and the alcohol at $C_{25}$ is also sterically hindered. Truncating the molecule at $C_{25}$ would preclude the formation of a chelate, and also lower the steric hindrance at the directing group. This steric reduction might mean that the catalyst would more selectively interact with the directing group over the enol ether.

(29) For the use of sodium alkoxide with **44**, see a) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232- 6233. For the use of sodium alkoxide with **43** on a substrate of comparable complexity, see: b) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937- 940.

(30) A chelate may also be formed with products **36** or **42**, involving the endocyclic ring of the pyran.

Selective hydrogenation of the trisubstituted olefin in **23** without hydrogenating the enol ether was unsuccessful.[31] The most noteworthy result was that catalyst **48** effected complete hydrogenation to compound **49** with high diastereoselectivity at $C_{23}$. (equation 4.4) The assignment of the stereochemistry is based solely on the Pfaltz model for similar substrates.[32] The enantiomer of **48** shown was the only one commercially available at the time, so this is why a catalyst predicted to produce the incorrect diastereomer was used. The other enantiomer of **48** is also readily available in a 5 step synthesis. This result is notable since it suggests that control of the configuration at $C_{23}$ is possible.[33] Use of this strategy in the synthesis would result in a less convergent synthesis, since fragment coupling at the enol ether would now have to occur before the hydrogenation, or possibly even before the olefin introduction. Consequently such an approach was held in reserve until all other options were explored.




Attention turned to alcohol **30**, with the thought that an alcohol would be a better directing group than an ester, and the trisubstituted olefin may also be a better backbonder than the enoate, allowing better selection between the olefins.

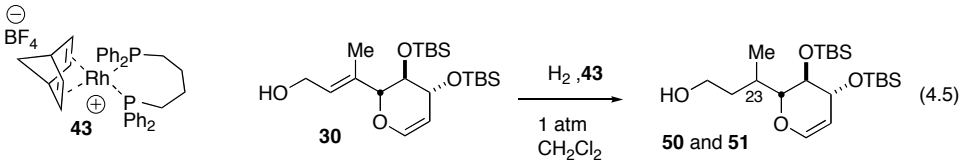
Allylic alcohol **30** was readily hydrogenated at ambient pressure using cationic rhodium catalyst **43** to yield a 1.2: 1 mixture of separable diastereomers at $C_{23}$, **50** and **51**, while

(31) As well as the catalysts in table 4.2, use of a chiral iridium *t*-Bu-PHOX catalyst and Rhodium DuPHOS based catalysts were attempted. Either no reduction or no olefin selectivity was observed. Stryker's reagent was also used in an attempt to do a conjugate reduction, but the reaction was unsuccessful.

(32) Manges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40- 44.

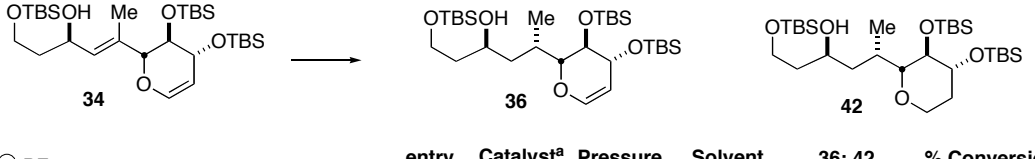
(33) Catalyst **40** did not hydrogenate either olefin of enoate **34** so the intrinsic diastereoselectivity could not be directly determined. The results in the next section suggest that the enoate does not have a strong facial bias, since alcohol **30** does not have a significant facial bias. Therefore hydrogenation of **23** with enantiomeric catalysts was not predicted to have matched and mismatched combinations.

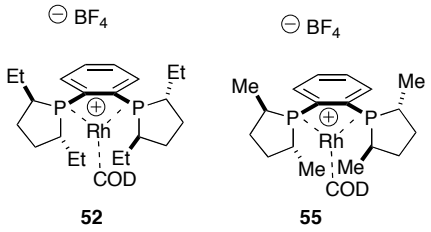
preserving the enol ether (equation 4.5). This result contrasts with the low activity of catalyst **43** with substrate **34** even at higher pressure, suggesting that steric factors are important for this catalyst's reactivity.




Encouraged by this result, chiral catalysts were screened, but these resulted in no hydrogenation at ambient pressure, and over hydrogenation at increased pressure.[34] Accordingly, one final hypothesis was investigated. In screening, Dr. Juhl had noted that chiral rhodium DuPHOS complexes appeared more reactive in his hydrogenation than Brown catalyst **43**, so the decision was made to retry the reduction of **34** using Rhodium *R,R*-Ethyl DuPHOS **52** (Table 4.3).

**Table 4.3** Conditions for selective hydrogenation of **34**.



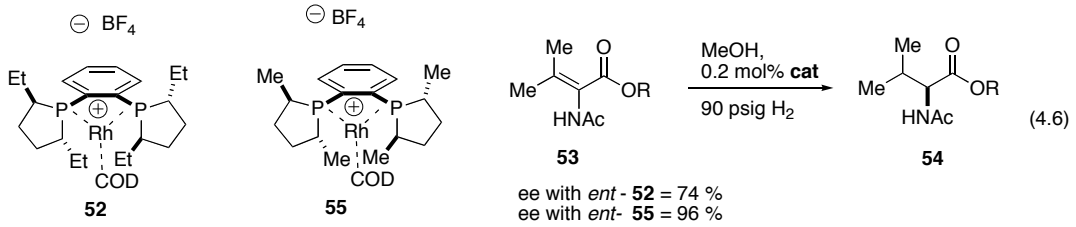

| entry | Catalyst[a] | Pressure | Solvent | 36: 42 | % Conversion |
|---|---|---|---|---|---|
| 1 | **52**[a] | 200 psig | $CH_2Cl_2$ | 1:0 | 60 % |
| 2 | **52**[a] | 800 psig | $CH_2Cl_2$ | 0:1 | 100 % |
| 3 | **55**[b] | 100 psig | $CH_2Cl_2$ | 1:0 | 99 % |
| 4 | **ent 55** | 100 psig | $CH_2Cl_2$ | n/a | 0 % |

a) 15 mol % catalyst
b) 2 mol% catalyst on 1.1 g scale

An initial experiment using 15 mol % loading of catalyst at 200 psig gave 60% conversion to the desired product with good selectivity (entry 1). Attempts to increase the conversion by increasing the pressure resulted in over reduction (entry 2). Inspection of

(34) Catalysts included: [Rh(nbd)(*R,R*-MeDuPHOS)]$BF_4$ (**55**), [Rh(COD)((-)-Binap)]$ClO_4$, $Ru(OAc)_2$((-)-Binap), **48**, [Ir(COD)(*t*-BuPhox)][3,5-BArF] and [Rh(nbd)((+)-DIOP)]$BF_4$. Only the last catalyst was active at ambient pressure, and no significant perturbation in diastereoselectivity was observed. Only one enantiomer of each catalyst was used, for reason of cost, and the enantiomer of the catalysts was chosen arbitrarily, with the exception of the Binap containing catalysts. For these, the enantiomer was chosen for which precedent existed that hydrogenation of geraniol would give the desired diastereomer. See: Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, S. A.; Inouye, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596- 1597.

the hydrogenation literature revealed that while the ethyl DuPHOS containing complexes are well suited to the hydrogenation of dehydroamino acids, they perform quite poorly in the hydrogenation of dehydro amino acids bearing tetrasubstituted double bonds, such as the hydrogenation of dehydrovaline **53** to valine **54** (equation 4.6). In cases such as this, *R,R*-Me DuPHOS catalyst **55** is superior.[35]




In the hydrogenation currently under consideration, the tri-substituted olefin in **34** has 2 substituents on the carbon of the olefin distal to the directing group, in analogy to the tetrasubstituted dehydroamino acids. Accordingly, *R,R*-Me DuPHOS catalyst **55** was employed in a hydrogenation reaction of **34**, which on the first attempt resulted in quantitative conversion and near perfect selectivity according to the crude proton NMR spectrum.

Upon scale- up, it was noted that some completely hydrogenated material was obtained. Typically each time the scale of hydrogenation increased, the loading of catalyst and pressure needed to be lowered to ensure good selectivity. The largest single batch hydrogenated was 1.5 g (out of a total of 10g of hydrogenation substrate prepared). No attempts to run the reaction on larger batches were made because at this point, a reproducible procedure had been found involving 2 mol% catalyst and there was no desire to consume further material in optimization (entry 3).[36]

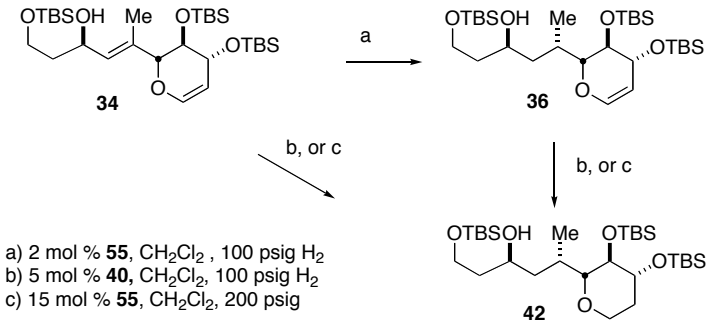
---

(35) a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375- 9376. b) Burk, M. *Acc. Chem. Res.* **2000**, *33*, 363- 372.

(36) Despite the 2 mol% loading, catalyst **55** was the single largest chemical expense in the course of this project. For larger reactions, investigation of the corresponding BPE catalysts, with a more flexible backbone, and higher reactivity may be warranted (see reference 35b). The cost of 500 mg of **55** is $432 from Strem as of May 2nd 2012. At the time of the hydrogenation studies, it would have been difficult to

One final note is on the stereochemistry of the hydrogenation product. Use of the *S, S*-Me DuPHOS catalyst **ent-55** under the same conditions resulted in no hydrogenation, indicating a substrate catalyst mismatch (entry 4). The product of the hydrogenation procedure using catalyst **55** was spectrally identical to that obtained in low yield using the achiral Crabtree's catalyst. The enol ether in hydrogenation product **36** could also be hydrogenated using Crabtree's catalyst **40**, or *R,R*-Me DuPHOS catalyst **55** at higher loading and pressure, to obtain **42**, the same product as when substrate **34** is exhaustively hydrogenated using Crabtree's catalyst in dichloromethane (Scheme 4.5).

**Scheme 4.5**

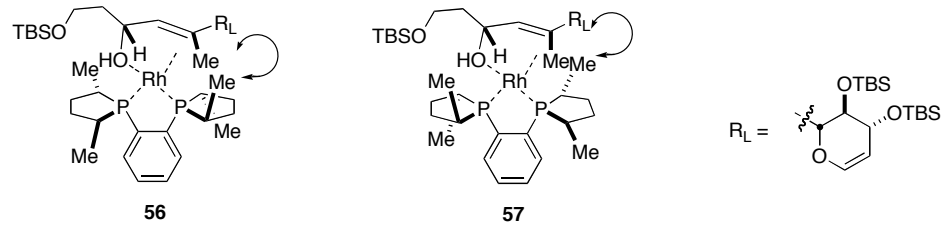



These results show that catalyst **55** hydrogenates from the same face that the substrate has a natural preference for. Employing the quadrant model for DuPHOS corroborates this, as shown in figure 4.4. Model **56** represents a matched case with *R,R*-DuPHOS, while model **57** represents the mismatched case with *S,S*-DuPHOS. It can be seen in model **56** that only the methyl group protrudes into the blocked quadrant, while in case **57** the large pyranyl group would protrude into the blocked quadrant.[37]

---

make **55** from DuPHOS ligand and a rhodium source on this small scale for a much lower price. With the recent decline in the price of rhodium salts, this approach may be warranted.

(37) This model makes the assumption that a Halpern type scenario, where the minor substrate-catalyst complex is more reactive and leads to the dominant hydrogenation product, is not active. See: Halpern, J. *Science*. **1982**, *217*, 401- 407. A number of examples suggest this Curtin-Hammet scenario is not operative in the directed hydrogenation of allylic alcohols. See: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307- 1370 and references therein.


TBSO
HO
H
Rh
Me
P
P
Me
Me
Me

and between the methyl group at $C_{23}$ and the proton at $C_{21}$. Since **58** is generated from pure **36**, the stereochemistry at $C_{23}$ on **36** may be inferred from this result. Two suggestions for the mechanism of formation of **58** are presented in scheme 4.6. In the first scheme, the enol ether in **36** complexes with an iridium (I) complex to form iridacyclopropane **59**, which in a ring-flipped all axial form may undergo an attack from the alcohol at $C_{25}$ to $C_{18}$, producing compound **60**. Compound **60** is poised to undergo an anti- β silyloxide elimination, with concomitant proton transfer to generate alkene **61**. Hydrogenation of **61** would result in the formation of **58**.

In an alternate mechanism, an iridium (III) hydride complex **62** protonates the OTBS group at $C_{20}$, resulting in the formation of oxocarbenium ion **63** and iridium (I) complex **64**. An intramolecular ether formation would result in the formation of alkene **61**. The proton from the alcohol at $C_{25}$ could protonate iridium (I) complex **64** at the metal, regenerating **62**, or it could protonate off a hydride, resulting in an iridium (I) cationic complex that would be poised to react with hydrogen again to regenerate **62**. Burgess has reported that iridium hydride complexes such as those intermediate in hydrogenations mediated by Crabtree's catalyst are acidic, and will react with enol ethers under certain conditions.[38]

## III. The First Fragment Coupling

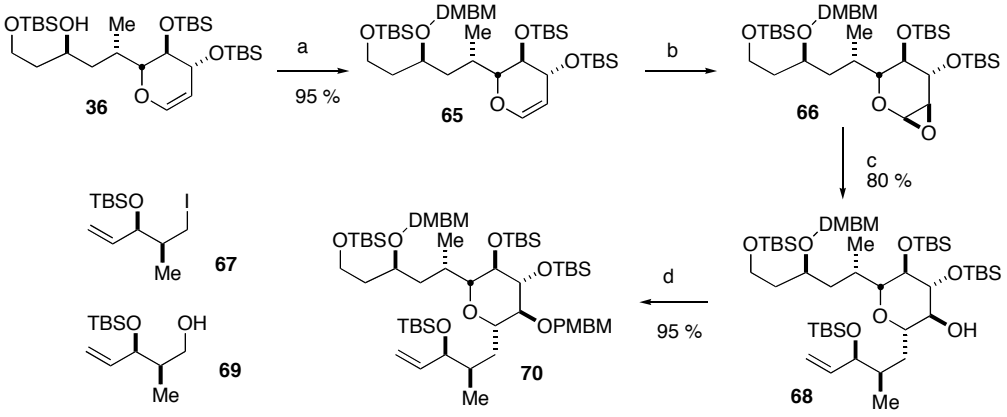
The $C_{25}$ alcohol of the hydrogenation product now had to be protected using a protecting group orthogonal to the TBS groups employed elsewhere in the synthesis. It is anticipated this alcohol will serve as a directing group for a hydrogenation a second time, after the ring closing metathesis reaction. It was decided to use a DMB group, which would be more readily removed than the PMBM group masking the alcohol at $C_{19}$ (the point of

(38) Zhu, Y.; Fan, Y.; Burgess, K. *J. Am. Chem. Soc.* **2010**, *132*, 6249- 6253.

installation of the sulfate). Unfortunately, efforts to install the DMB group using either DMB bromide or DMB trifluoroacetimidate were unsuccessful. Gratifyingly, the more reactive DMBM chloride allowed the installation of a DMBM group to afford **65**, which should have the same oxidative advantage over the PMBM group (Scheme 4.7).[39]

With the protected hydrogenation product **65** in hand, the next major reaction was applying the coupling of an organocuprate to the glycal epoxide as used by Juhl in the prior route. DMDO was used to oxidize compound **65**, which produced epoxide **66** very cleanly, allaying fears that the electron rich DMBM group would be oxidized. [40,41] It was noted that batches of DMDO that were wet did not have any detrimental effect on the yield (the glycal epoxide is dried via benzene azeotrope, and any droplets of water were removed manually from the benzene solution by pipette). Accordingly, molecular sieves were not used to dry the DMDO.

**Scheme 4.7**




a) $SO_2Cl_2$, $DMBOCH_2OCH_2SCH_3$, $CH_2Cl_2$, -78 °C, then **36**, TBAI, *i*-$Pr_2NEt$, $CH_2Cl_2$, 40 °C;
b) DMDO, $CH_2Cl_2$, acetone, 0 °C; c) *t*-BuLi, **67**, $MgBr_2$, $Et_2O$, -78 °C, then $Li_2CuCl_4$, THF, then **66;**
d) $SO_2Cl_2$, $PMBOCH_2OCH_2SCH_3$, $CH_2Cl_2$, -78 °C, then **68**, TBAI, *i*-$Pr_2NEt$, $CH_2Cl_2$, 40 °C;

(39) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666- 3667.

(40) For the preparation of DMDO, see Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, 2377.

(41) The seminal preparation of anhydrosugars by DMDO oxidation: (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666. For studies on the facial selectivity of this reaction: (b) Alberch, L.; Cheng, G.; Seo, S.-K.; Li, X, Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2011**, *76*, 2532- 2547.

More crucially standing the DMDO over sodium carbonate was obligatory. Omission of this step resulted in complete decomposition of the glycal epoxide. *In-situ* preparations of DMDO did not give a clean reaction.[42]

Adaptation of the epoxide opening procedure of Juhl to glycal epoxide **66** was completely uneventful.[43] Iodide **67** , available from work on the project by Dr. Juhl and Dr. Pero was employed as the coupling partner to provide fragment coupling product **68**. Glycal **65** was noted as a minor byproduct, despite complete oxidation by DMDO in the earlier step. An equal amount of alcohol **69** was noted, and it seems a reasonable explanation is a reduction of the epoxide by either the Grignard reagent or organocuprate during the course of the reaction. The product of the ring opening was protected as the PMBM ether according to the precedent of Juhl. This totally protected compound **70** provided a good place to store material along the route, as the absence of any alcohols precluded protecting group migration, and no epimerizable stereocentres are present.

## IV. Elaboration to β-Ketophosphonate

Elaboration of this compound to a β-ketophosphonate was enabled by a 3 step procedure, according to the precedent of Borg and Juhl. Exposure of compound **70** to ozone proved problematic, as decomposition of the DMBM group was noted even in the presence of Sudan III or Sudan black dyes (Scheme 4.8).[44] Fortunately acceptable yields were obtained upon addition of pyridine to the ozonolysis mixture.[45] The quantity of pyridine

(42) Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydrate Res.* **2006**, *341*, 2714- 2716.

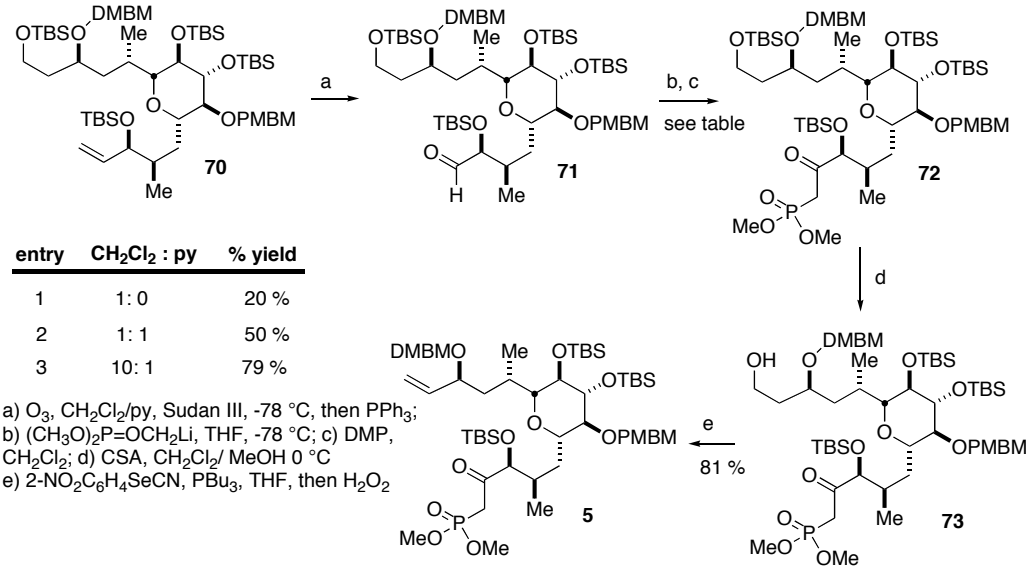
(43) Klein, L. L.; McWhorter, W. W.; Ko, S. S.; Pfaff, K.-P.; Kishi, Y. Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7362- 7364.

(44) Incompatibility of methoxybenzyl groups with ozonolysis has been noted: Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.*, **2004**, *6*, 3217- 3219.

(45) For the seminal report of adding pyridine to ozonolysis reactions of sensitive substrates: Slomp Jr., G.; Johnson, J. L.; *J. Am. Chem. Soc.* **1958**, *80*, 915- 921.

was important, with too much being detrimental to yield.[46] Besides behaving as a base, it is possible that pyridine may π stack with the electron rich DMBM and PMBM groups, reducing their richness and propensity to react with ozone. The sensitive aldehyde **71** was used without further purification in the next step, the addition of an excess of the lithium anion of dimethyl methyl phosphonate.[47] The next step was the oxidation of the inconsequential mixture of diastereomers with Dess–Martin periodinane to form the β–ketophosphonate **72**. It was noted the Parikh–Doering conditions result in no oxidation of this substrate.

**Scheme 4.8**




| entry | $CH_2Cl_2$ : py | % yield |
|---|---|---|
| 1 | 1: 0 | 20 % |
| 2 | 1: 1 | 50 % |
| 3 | 10: 1 | 79 % |

a) $O_3$, $CH_2Cl_2$/py, Sudan III, -78 °C, then $PPh_3$;
b) $(CH_3O)_2P{=}OCH_2Li$, THF, -78 °C; c) DMP, $CH_2Cl_2$; d) CSA, $CH_2Cl_2$/ MeOH 0 °C
e) 2-$NO_2C_6H_4SeCN$, $PBu_3$, THF, then $H_2O_2$

Since the alkene formerly in the molecule had been exploited as a latent aldehyde at this point, it was now possible to reveal the latent alkene, which will participate in the ring closing metathesis. The silyloxy ether at $C_{26}$, of compound **72** was accordingly deprotected to yield alcohol **73**. This alcohol/ phosphonate was found to be extremely

(46) Pyridine is resistant to oxidation by ozone, however allowing ozonides to warm in the presence of pyridine without adding a reductant may be detrimental to yield: Griesbaum, K. *Chem. Comm*. **1966**, *24*, 920- 921. For a recent exploitation of pyridine as an agent to disproportionate ozonides catalytically, see: Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H.; *Org. Lett*. **2012**, *14,* 2242-2245. It is possible this disproportionation is responsible for the lower yield above when a larger percentage of pyridine is used in the solvent mixture.

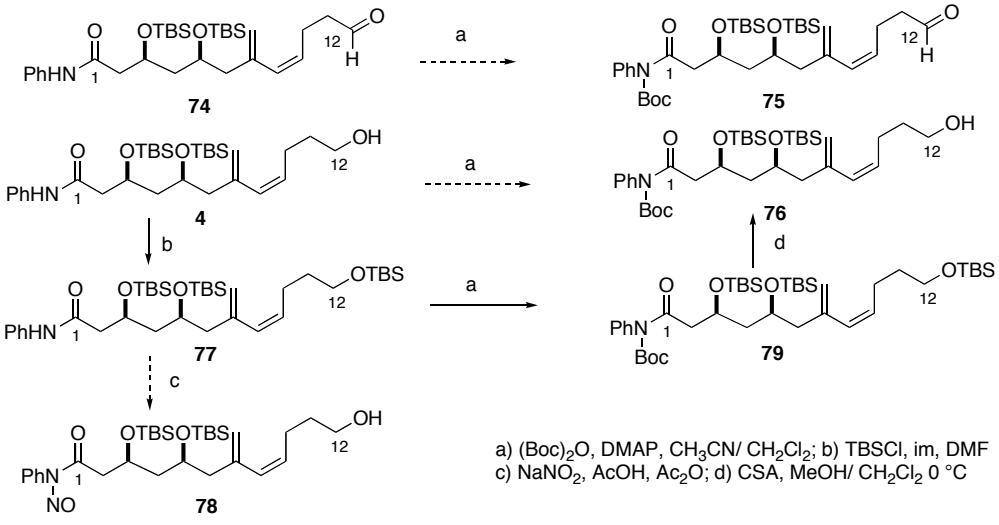
(47) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654- 5656.

polar, and was usually carried on to the next reaction without any further purification. A one pot Grieco elimination provides alkene **5**, which also proved to be stable to long term storage.[48]

## V. Elaboration of the Borg/ Bindschädler Diene Fragment

In the key fragment coupling developed over several iterations by Borg, Juhl and Pero, and described in chapter 3, fragment **74**, containing the diene and terminated with an aldehyde, was reacted with a pyran containing phosphonate in a HWE reaction to form $C_{12}$–$C_{13}$ bond. The resulting enone was reduced using Luche conditions under Felkin control. The allylic alcohol was transiently protected as a TMS ether so that the *N*-Phenyl amide can be Boc protected to activate it for cleavage. It was envisioned that the convergency of this approach could be improved by BOC protection of the *N*-phenyl amide before the HWE reaction. This would obviate the need for transient protection of the Luche product. The diene containing fragment **4** used in these studies was prepared by Dr. Pascal Bindschädler by the route developed by Dr. George Borg, and I carried out the initial studies for functionalization of the *N*-phenyl amide shown in scheme 4.9.

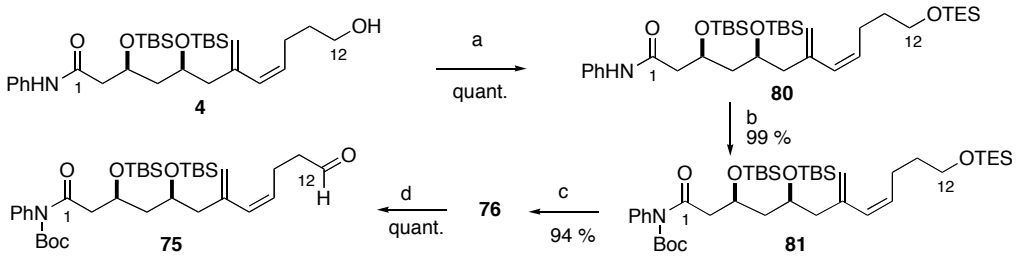
**Scheme 4.9**




(48) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.,* **1976**, *41*, 1485- 1486.

Initial attempts to Boc protect aldehyde **74** to produce aldehyde **75** led to decomposition. Moving to free alcohol **4**, attempts to introduce a Boc group also led to decomposition rather than Boc amide **76**. Alcohol **4** was silylated to give compound **77**. This could be Boc protected cleanly. Attempts to nitrosate the *N*-phenyl amide on compound **77**, which would lead to a functionally equivalent *N*-nitrosoamide **78** led to decomposition of the diene moiety.[49] The initial sequence was performed using a TBS group as the transient protection. This sequence was subsequently scaled up and optimized by Dr. Bindschadler, who employed a TES group to form intermediate **80**. The removal of the TES group from intermediate **81 is** much more efficient (Scheme 4.10). I also conducted oxidation of alcohol **76** aldehyde to aldehyde **75**.

**Scheme 4.10**




a) TESCl, im, $CH_2Cl_2$, 0 °C; b) $(Boc)_2O$, DMAP, $CH_3CN$/ $CH_2Cl_2$; c) PPTS, MeOH/ $CH_2Cl_2$ 0 °C; d) DMSO, $SO_3$•py, *i*-$Pr_2NEt$, $CH_2Cl_2$

## VI. The Second Fragment Coupling and Elaboration to Macrolactone 3

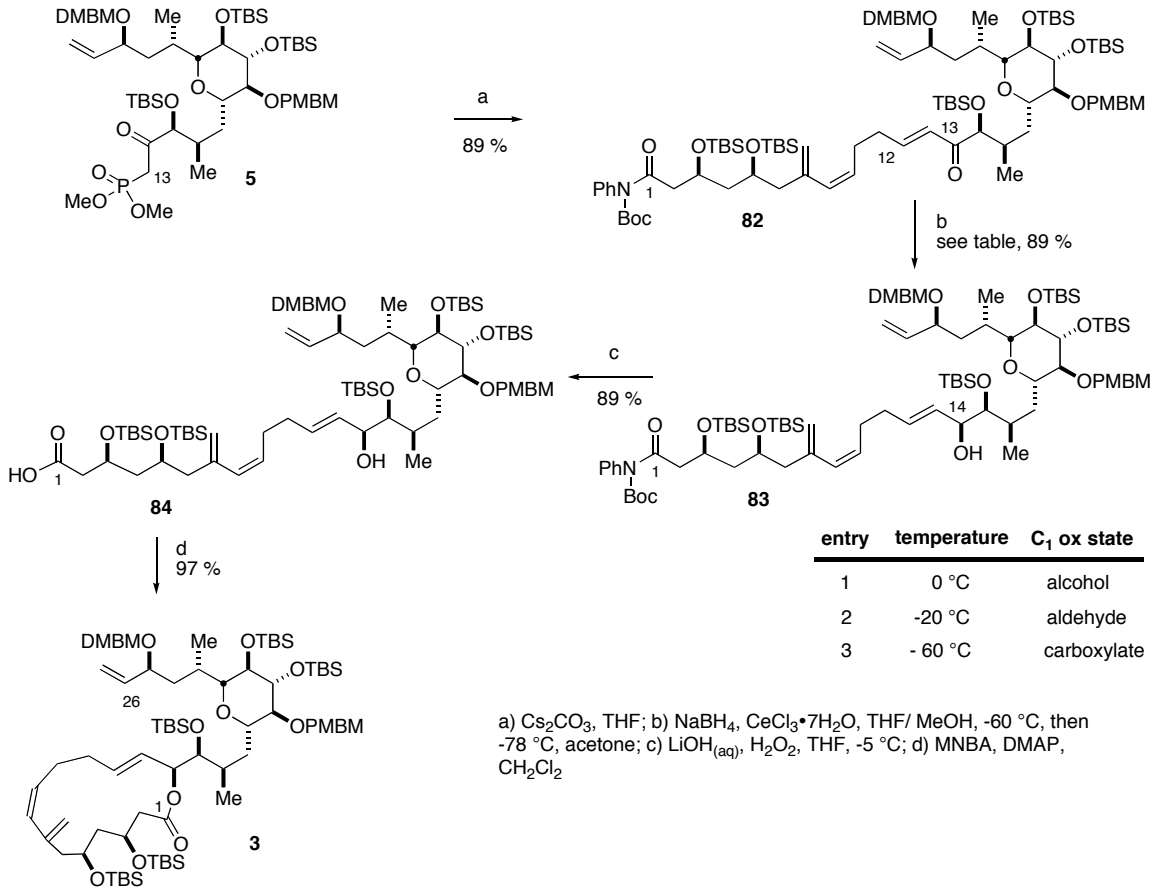
The aldehyde containing fragment **75** was coupled with phosphonate **5** in an uneventful HWE reaction to yield enone **82** (Scheme 4.11). The *E* to *Z* ratio was higher than 20: 1. Both *n*-butyllithium and cesium carbonate could be employed as bases with similar outcome of olefin geometry, though the presence of more uncharacterized polar compounds was noted with the use of cesium carbonate. Initially, an excess of the aldehyde was used, as only small quantities of the phosphonate had been prepared. After the large scale preparation of the phosphonate, it was employed in excess since the

(49) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron. Lett.* **1997**, *38*, 4535- 4538.

aldehyde was deemed more precious despite the shorter step count. Fortunately excess phosphonate or aldehyde could cleanly be recovered from either stoichiometry.

The subsequent Luche reduction required some optimization. Use of the conditions initially employed by Juhl at 0 ºC resulted in clean reduction of both the $C_{14}$ ketone, and the *N*-Phenyl Boc protected imide at $C_1$ to the corresponding alcohols.

**Scheme 4.11**




| entry | temperature | $C_1$ ox state |
|---|---|---|
| 1 | 0 °C | alcohol |
| 2 | -20 °C | aldehyde |
| 3 | - 60 °C | carboxylate |

Reduction at -20 ºC resulted in the formation of a new product that initially did not contain free Boc aniline, but released that compound and contained an aldehyde after chromatography. It was speculated that a stable hemiaminal was formed. Finally, conditions were found where the reaction was allowed to proceed at -60 ºC for one hour, with a subsequent acetone quench at -78 ºC, giving alcohol **83** cleanly. Optimization of

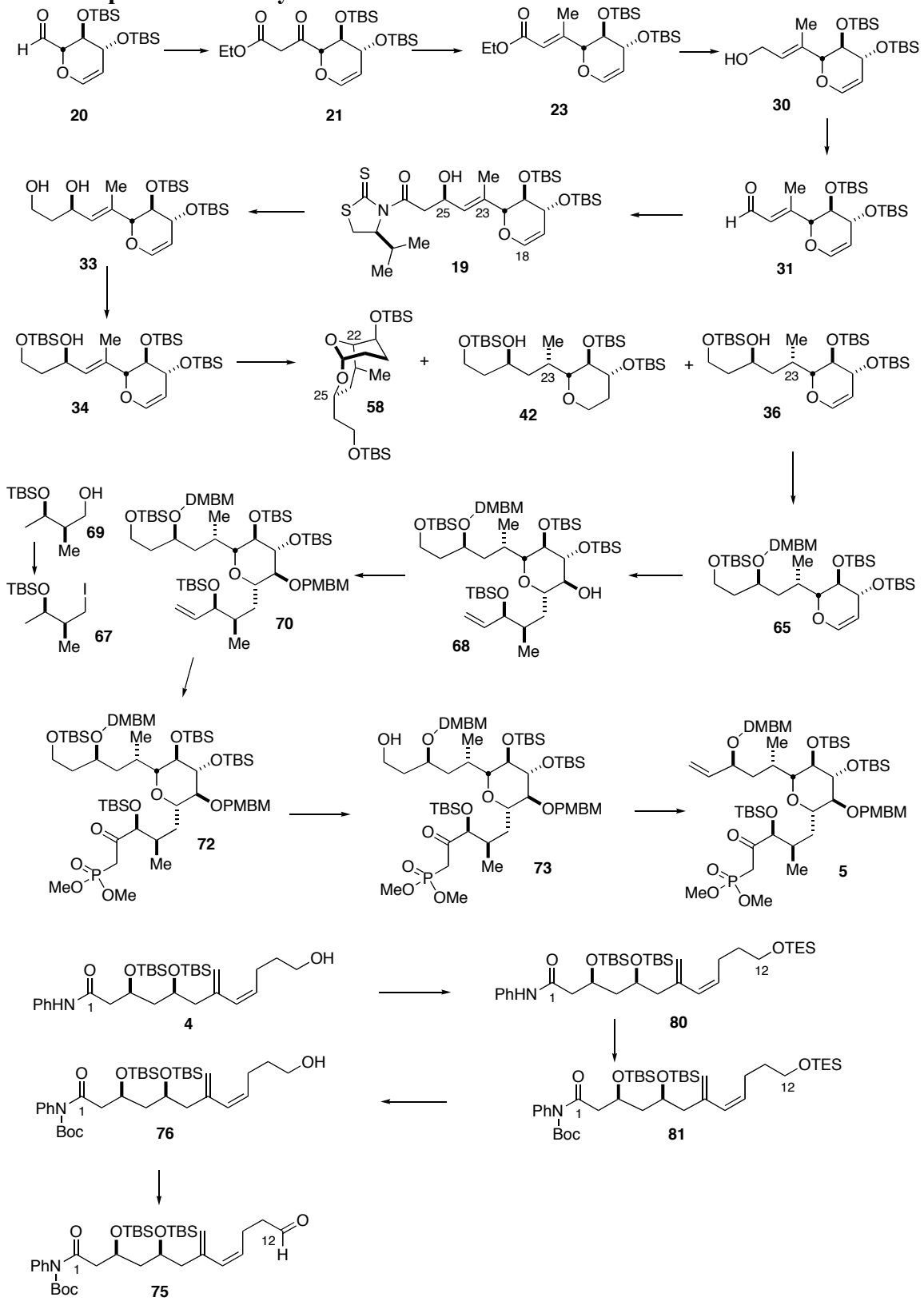
this reaction was complicated by the fact that the enone and allylic alcohol had the same $R_f$ in a variety of solvents, and that the reaction readily proceeded to exhaustive reduction in the TLC spotter. The cleavage of the imide was uneventful. The seco acid **84** was quite non polar, especially in comparison to the peloruside A seco acid, and could be readily purified by column chromatography. Macrolactonization proceeded readily under the Shiina conditions used by Dr. Juhl to give macrolactone **3**.[50]

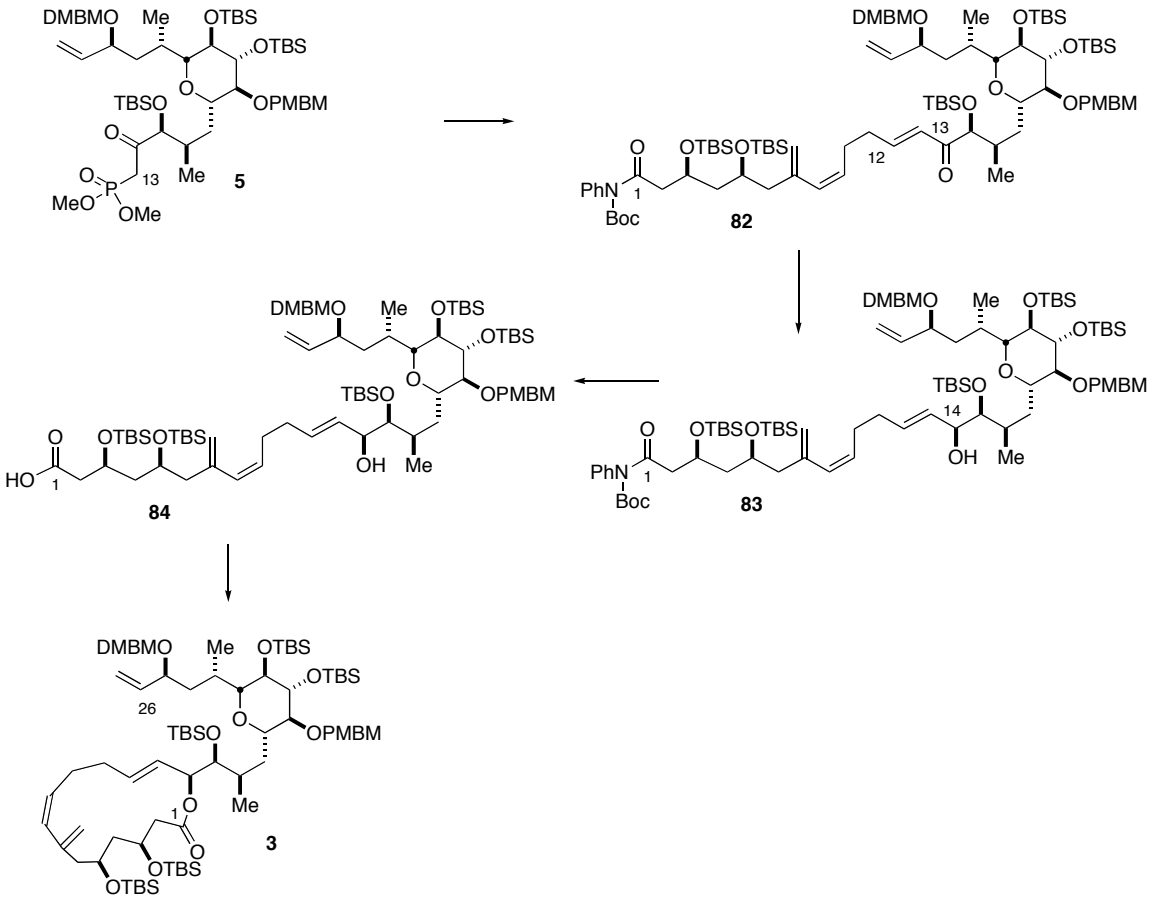
**VII. Conclusion**

An approach to fragment **3** which contains a *Z* diene macrolactone, an appropriately protected pyran and a handle for olefin metathesis was completed. The approach was able to conserve key disconnections developed in previous work on the project, namely a diastereoselective hydrogenation, a glycal epoxide opening by an organocuprate and a HWE reaction. Notable accomplishments involved the replacement of a Stille coupling using stoichiometric palladium with an iron mediated cross coupling, and the optimization of a difficult hydrogenation of a trisubstituted double bond in the presence of an enol ether.

(50) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron. Lett.* **2002**, *43*, 7535- 7539.

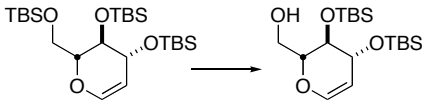
## VIII. Graphical Summary




DMBMO
Me
OTBS
OTBS
TBSO
OPMBM
O
MeO
P
OMe
13
Me
5
PhN
Boc
1
OTBSOTBS
12
13
82
14
83
84
HO
OH
26
1
3

## IX. Experimental Section

### ((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)methanol (S2)

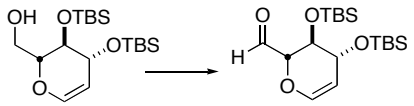



**S1** **S2**

While higher yields were reported in the literature for the preparation of this starting material, the indicated conditions were chosen to avoid the use of copious quantities of HF-Pyridine at an early stage in the synthesis.

A solution of **S1** (42.0g, 85.9 mmol)[11a] in 120 mL MeOH and 36 mL $CH_2Cl_2$ at room temperature was treated with PPTS (1.08g, 4.29 mmol, 0.05 eq). The reaction was stirred for 45 hours, then quenched by addition of 10 mL saturated $NaHCO_3$. The solution was diluted with 500 mL of 90% EtOAc/hexanes, and washed with 100 mL water. The aqueous layer was extracted 2x with 100 mL of 90% EtOAc and hexanes. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% to 10% EtOAc/ Hexanes) afforded 13.1 g (37.6 mmol, 44%) of alcohol **S2** as a white waxy solid. This material was judged to be of >95 % purity by $^1$H NMR analysis. Analytical data was in accordance with literature values.[11a]

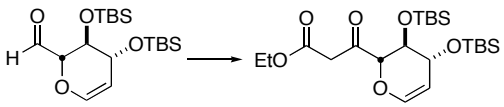
**(2*S*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-carbaldehyde (20)**




**S2** **20**

Alcohol **S2** (12.2g, 32.6 mmol) was dissolved in 108 mL $CH_2Cl_2$ and Hunig's base (17 mL, 98 mmol, 3.0 eq) and dimethyl sulfoxide (14 mL, 200 mmol, 6.0 eq) were added sequentially. The resulting pale yellow mixture was cooled to 0 °C. $SO_3$- Pyridine (10.4g, 65.1 mmol, 2.0 eq) was added, briefly removing the septum. After 15 minutes, TLC analysis showed completion. Volatiles were removed *in vacuo* and the resulting residue was taken up in a minimal amount of $CH_2Cl_2$ and loaded on a pre-equilbrated column which was eluted using 5% EtOAc/hexanes to afford 11.6g (31.1 mmol, 95% ) of aldehyde **20** as a free flowing tan powder. This material was judged to be of >95 % purity by $^1$H NMR analysis. Analytical data was in accordance with literature.[11b]

**ethyl 3-((2*S*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)-3-oxopropanoate (21)**




**20** **21**

Note: The following procedure was conducted behind a blast shield out of an abundance of caution. This reaction was conducted 6 times on scales larger than 1g without incident. The following represents the largest batch we prepared. Stannous chloride may also be used as the catalyst, with a slight decrease in yield. It is essential that the starting aldehyde be free of DMS or DMSO for this reaction to initiate properly. Niobium pentachloride (71 mg, 0.266 mmol, 0.01 eq) was quickly ground into a fine powder and placed in a dry 250 mL round bottom flask, equipped with a large egg shaped stirbar, with no septum but with a stream of nitrogen blowing through the neck of the flask. The

rate of nitrogen flow is such that the dichloromethane used in the reaction solvent is removed. Ethyl diazoacetate (5.60 mL, 53.2 mmol, 2.0 eq) was added to the flask. Bubbling ensued for several seconds then ceased and a reddish suspension formed. A digital thermocouple was immersed in the ethyl diazoacetate to allow monitoring of the internal temperature. Aldehyde **20** (9.90 g, 26.6 mmol) was dissolved in a minimal amount of $CH_2Cl_2$ (10 mL). Using a glass pipette, 1 mL of this solution was added to the suspension. Depending on the ambient temperature, the reaction may initiate spontaneously, or may require heating. In this case, no reaction spontaneously occurred after 5 minutes, so the flask was cautiously heated with a heat gun on its lowest setting until the internal temperature reached 35 °C. At this point bubbling was observed, and the internal temperature rose to 40 °C. The remaining solution of aldehyde **20** was added at a rate such that this temperature was not exceeded (over approximately 15 minutes). After approximately half the aldehyde had been added, the bubbling slowed, so another sample of powdered Niobium pentachloride (71 mg, 0.27 mmol, 0.01 eq) was added. This caused vigorous foaming, that was readily contained in the 250 mL flask. After completion of the aldehyde addition, the reaction was stirred until bubbling ceased (approximately 45 minutes). TLC (10% EtOAc/ hexanes, product stains brownish/yellow by anisaldehyde visualization) showed complete consumption of starting material. The reaction was quenched by dilution with 100 mL $CH_2Cl_2$ and the addition of 25 mL saturated $NaHCO_{3(aq)}$. The layers were separated and the aqueous layer was washed with 50 mL of $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo* on a rotavap contained within a fumehood. Purification by flash chromatography over silica gel (0.5% –> 1% –-> 2% EtOAc/ hexanes) afforded 10.0 g (21.8 mmol, 82%) of β-ketoester **21** as a pale yellow liquid. β-ketoester **21** conveniently eluted before the yellow band of the excess ethyldiazoacetate . This material was judged to be of >95 % purity by $^1$H NMR analysis, some signals attributed to enol content were observed.

$R_f$ = 0.20 (5% EtOAc/hexanes, UV active, stains brown in anisaldehyde)

$[\alpha]^{20}_D$ = -42.2 (*c* 2.00, $CHCl_3$);

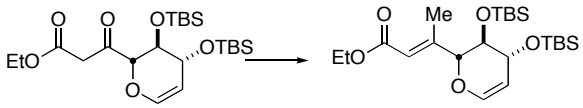
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.49 (d, *J* = 6.30 Hz, 1H), 4.39 (td, *J* = 4.8, 1.0 Hz, 1H), 4.49 (s, 1H), 4.20- 4.15 (m, 3 H), 3.84 (app. d, *J* = 16.4 Hz, 1H), 3.77- 3.74 (m, 1H), 3.31 (app. d, *J* = 16.4 Hz, 1H), 1.26 (td, *J* = 7.2, 0.6 Hz, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.3, 167.5, 143.4, 102.0, 82.5, 70.8, 63.7, 61.4, 46.4, 25.9 (2 signals), 18.2 (2 signals), 14.3, -4.4, -4.5, -4.6, -4.9;

IR(film) 2954.9, 1747.9, 1724.8, 1650.2, 1472.0,1252.2, 1098.0, 1061.8 $cm^{-1}$;

Exact Mass Calc. for $C_{22}H_{42}O_6Si_2$ $[M + Na]^+$ : 481.24121 found; 481.24107 (ESI)

**(*E*)-ethyl 3-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)but-2-enoate (23)**




Sodium hydride (95%, mineral oil free, 0.619g, 25.8 mmol, 1.5 eq ) was suspended in 10 mL THF in a 500 mL RBF under nitrogen. A digital thermocouple was placed through the septum to monitor the internal temperature. β-ketoester **21** (7.9 g, 17.2 mmol) was dissolved in 25 mL THF under nitrogen and transferred to the sodium hydride suspension using a syringe and needle. An additional 5 mL + 5 mL THF were used to quantitate the

transfer. The pale brown suspension was stirred for fifteen minutes until bubbling ceased. At this point, an additional 20 mL of THF were added, and the flask was cooled to -78 °C. Freshly distilled triflic anhydride (2.9 mL, 17.2 mmol, 1.0 eq) was added dropwise such that the internal temperature did not rise above -55 °C. After 20 minutes, TLC analysis (10% EtOAc/ toluene, triflate stains blue by anisaldehyde visualization, $R_f$ =0.85) shows complete consumption of the beta keto ester ($R_f$ = 0.7). To the reaction mixture is added an additional 100 mL of THF, followed by a solution of iron (III) acetylacetonate (607 mg, 1.72 mmol, 0.10 eq) in 15 mL NMP. The resulting orange solution is warmed to an internal temperature of -30 °C (using acetone with dry ice added to maintain the appropriate temperature). Methylmagnesium chloride (3.0 M in THF, 11.4 mL, 24.4 mmol, 2.0 eq) is added dropwise at such a rate to maintain the temperature below -20 °C (brief excursions to -10 °C have not been detrimental to yield). The resulting deep green suspension is stirred at -30 °C until TLC shows the consumption of the enol triflate intermediate (10 % EtOAc/ toluene, product stains blue/purple by anisaldehyde visualization, $R_f$ =0.90). Note that eluants based on hexanes as the non-polar phase to not allow seperation of the enol triflate and the product, potentially resulting in a premature quench. The reaction typically is complete in under 20 minutes. The reaction was quenched by the addition of 50 mL saturated $NH_4Cl_{(aq)}$, briefly stirred, and transferred to a separatory funnel containing an additional 50 mL of water and 250 mL of 90% EtOAc/ hexanes. This was immediately shaken, restoring an orange colour to the solution. The layers were separated and the aqueous layer was washed with 2x 100 mL of 90% EtOAc/hex. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% EtOAc/ hexanes) afforded 7.23 g (15.8 mmol, 92%) of enoate **23** as a viscous colourless liquid.

$R_f$ = 0.55 (10 % EtOAc/hexanes, UV active, stains blue/purple with anisaldehyde)

$R_f$ = 0.90 (10 % EtOAc/toluene)

$[\alpha]^{20}_D$ = -28.6 (*c* 2.28, $CHCl_3$);

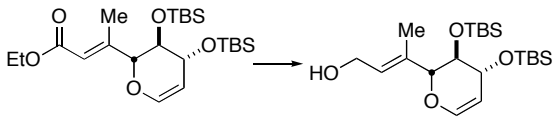
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.43 (d, *J* = 6.2 Hz, 1H), 5.83 (s, 1H), 4.74 (apt. t, *J* = 4.2 Hz, 1H), 4.34 (d, *J* = 4.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.99- 3.95 (m, 2H), 2.15 (s, 3H), 1.25 (t, *J* = 7.1, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.5, 152.9, 143.2, 116.5, 102.1, 82.2, 70.8, 67.3, 59.6, 25.8, 25.7, 18.1, 18.0, 16.0, 14.3, -4.2 (3 signals), -4.7

IR(film) 2930.0, 2857.7, 1720.1, 1649.2, 1472.0, 1251.0, 1096.6, 836.7, 776.8 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{44}O_5Si_2$ $[M + Na]^+$ : 479.26195 ; found : 479.26353 (ESI)

**(*E*)-3-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)but-2-en-1-ol (30)**




Enoate **23** (4.43g, 9.69 mmol ) was dissolved in 60 mL $CH_2Cl_2$ in a 250 mL flask equipped with a thermocouple and an egg shaped stirbar under nitrogen. The resulting solution was cooled to -78 C and DiBAlH (1.0 M in toluene, 20.4 mL, 20.4 mmol, 2.1 eq ) was added over 10 minutes at such a rate as to keep the internal temperature below -70 °C. After 10 minutes, TLC analysis (20 % EtOAc, SM and product visualize as blue in CAM) showed complete consumption of starting material. The reaction was quenched at

-78 °C with a mixture of 60 mL saturated Rochelle's salt and 10 mL MeOH and allowed to warm to room temperature. The resulting biphasic mixture was stirred for 3 hours, until both layers were clear. The layers were separated, and the aqueous layer was extracted with 2x 100 mL $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% to 20% to 40% EtOAc/ hexanes) afforded 3.570g (8.60 mmol, 89%) of allylic alcohol **30** as a very viscous colourless liquid.

$R_f$ = 0.60 (30% EtOAc/hexanes, stains blue in CAM)

$[\alpha]^{20}_D$ = -62.3 (*c* 1.80, $CHCl_3$);

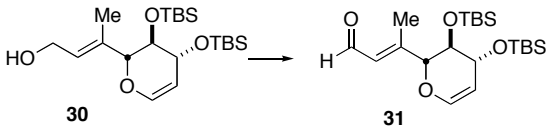
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.35 (d, *J* =6.2 Hz, 1H), 5.67 (t, *J* = 6.4 Hz, 1H), 4.68 (dd, *J* = 6.2, 3.1 Hz, 1H), 4.22 (td, *J* = 12.4, 3.3 Hz, 1H), 4.19- 4.14 (m, 2H), 3.81 (dd *J* = 7.2, 5.1 Hz, 1H), 1.69 (s, 3H), 0.59 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.04 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 143.6, 134.4, 128.0, 103.1, 83.6, 71.8, 70.2, 59.6, 26.3, 26.1, 18.5, 18.4, 13.3, -3.4 (2 signals), -2.6, -4.4;

IR(film) 3366.2, 2930.0, 2857.9, 2360.1, 1635.6, 1472.9, 1257.7, 1112.6, 1006.2, 836.6, 777.0 $cm^{-1}$;

Exact Mass Calc. for $C_{21}H_{42}O_4Si_2$ $[M + Na]^+$ : 437.25138 ; found : 437.25241(ESI)

**(*E*)-3-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)but-2-enal (31)**



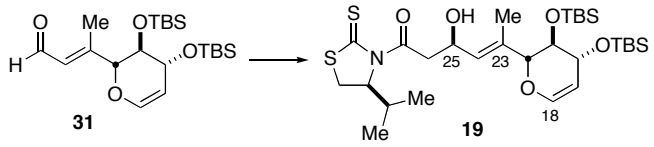

Allylic alcohol **30** (3.57 g, 8.60 mmol) was dissolved in 30 mL $CH_2Cl_2$ under nitrogen and Hunig's base (4.65 mL, 25.9 mmol, 3.0 eq) and dimethyl sulfoxide (3.6 mL, 51.7 mmol, 6.0 eq) were added sequentially. The resulting pale yellow mixture was cooled to 0 °C. $SO_3$- Pyridine (2.26 g, 17.2 mmol, 2.0 eq) was added, briefly removing the septum. After 15 minutes, TLC analysis showed completion. Volatiles were removed *in vacuo* and the resulting residue was taken up in a minimal amount of $CH_2Cl_2$ and loaded on a pre-equilbrated column which was eluted using 5% EtOAc/hexanes to afford 3.36g (8.14 mmol, 95% ) of aldehyde **31** as viscous off yellow liquid. This material was judged to be of >95 % purity by $^1$H NMR analysis. Aldehyde **31** was not particularly stable, and was typically prepared during the enolization step of the next reaction and used immediately. In order to achieve a high diastereoselectivity in the acetate aldol reaction, aldehyde **31** must be free of ligating impurities such as DMS or DMSO.

Partial Characterization Data:

$R_f$ = 0.95 (30 % EtOAc/hexanes, UV active, stains blue in CAM)

$^1$H NMR (600 MHz, $CDCl_3$) δ 10.02 (d, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 6.1 Hz), 6.03 (dt, *J* = 7.9, 1.3 Hz, 1H), 4.76 (td, *J* = 4.7, 1.2 Hz, 1H), 4.58- 4.47 (m, 1H), 4.02 (ap. t, *J* = 4.4 Hz, 1H), 3.94 (ap. t, *J* = 4.4 Hz, 1H), 2.20 (s, 3H), 0.90 (s, 9H), 0.84 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H);

**(*R*,*E*)-5-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)-3-hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)hex-4-en-1-one (19)**




$Sn(OTf)_2$ (3.74g, 8.97 mmol, 1.1 eq), prepared according to a modified procedure of Weber, was placed in a 250 mL flask and suspended in 30 mL $CH_2Cl_2$. The suspension was cooled to -30 °C in a cryocool and *N*-ethylpiperidine (1.23 mL, 8.97 mmol, 1.1 eq) was added. The resulting light yellow turbid solution was stirred for 5 minutes, then a solution of thiazolidinethione **17** (1.99g, 9.79 mmol, 1.2 eq) in 10 mL $CH_2Cl_2$ was added dropwise by syringe. An additional 5 mL $CH_2Cl_2$ was used to rinse the flask and syringe containing thiazolidinethione **17**. After one hour, the resulting orange suspension was cooled to -78 C and aldehyde **31** (3.36g, 8.14 mmol) dissolved in 10 mL $CH_2Cl_2$ is added dropwise. A futher 5 mL DCM is used to rinse the flask and syringe containing aldehyde **31**. After 1 h, TLC appears to show no further conversion so the reaction is quenched by the addition of 30 mL saturated $NH_4Cl_{(aq)}$. The resulting suspension is stirred for 10 minutes, and the resulting tin oxide is removed by filtration through Celite® . The Celite® and tin oxide are washed with 100 mL $CH_2Cl_2$. The layers are separated, and the aqueous layers are extracted 2x 50 mL $CH_2Cl_2$. . The combined yellow organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% to 20 % to 50 % EtOAc) enabled the recovery of 300 mg (0.73 mmol, 9%) of the starting aldehyde. Unreacted acetylthiazolidinethione could also be recovered, eluting between the aldehyde and the aldol adduct. Aldol adduct **19** 4.61 g (7.5 mmol, 91%, ) was obtained as a bright yellow foam, collapsing to a tacky solid. $^1H$ NMR shows the aldol adduct to be a 13: 1 mixture of diastereomers, which were not separable by chromatography.

$R_f$ = 0.40 (30% EtOAc/hexanes, UV active, stains dark purple with Anisaldehyde)

$[\alpha]^{20}_D$ = +140.3 (*c* 2.18, $CHCl_3$);

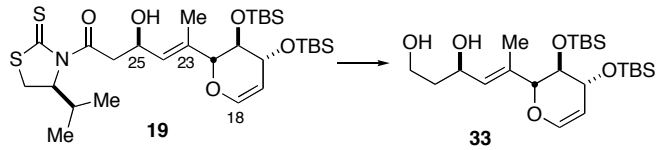
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.34 (dd, *J* = 6.2, 1.2 Hz, 1H), 5.55 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.14 (td, *J* = 6.3, 0.9 Hz, 1H), 4.96- 4.91 (m, 1H), 4.67 (dd, *J* = 6.2, 2.9 Hz, 1H), 4.17- 4.15 (m, 1H), 4.14 (d, *J* = 7.3 Hz, 1H), 3.81 (dd, *J* = 7.5, 5.3 Hz, 1H), 3.55 – 3.36 (m, 3H), 3.03 (dd, *J* = 11.6, 1.0 Hz, 1H), 2.77 (s, 1H), 2.54 (d, *J* = 4.3 Hz, 1H), 2.37 (app. septet, *J* = 6.4 Hz, 1H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.06 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.0, 172.8, 143.6, 134.6, 130.0, 103.3, 83.8, 71.9, 71.7, 70.5, 65.1, 45.5, 31.1, 31.0, 26.4, 26.2, 19.3, 18.5, 18.4, 16.1, 13.7, -3.3, -3.4, -3.5, -4.3;

IR(film) 3508.3, 2955.7, 1691.8, 1650.1, 1471.4, 1361.7, 1253.4, 1159.8, 1120.8, 1093.8, 836.6, 778.0 $cm^{-1}$;

Exact Mass Calc. for $C_{29}H_{53}NO_5S_2Si_2$ $[M + Na]^+$ : 638.27959 ; found : 638.27982 (ESI)

**(*R*,*E*)-5-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)hex-4-ene-1,3-diol (33)**




Aldol adduct **19** (4.61g, 7.48 mmol) was dissolved in a mixture of 75 mL THF and 7.5 mL $H_2O$. The resulting yellow solution was cooled to an internal temperature of -18 °C (ice/acetone bath). Lithium borohydride (2.0 M solution in THF, 3.74 mL, 7.48 mmol, 1

eq) was added. After 30 minutes, the yellow colour had faded and TLC (30 % EtOAc/ hex, CAM visualizes SM as purple, product as blue, product $R_f$ 0.15) showed complete consumption of starting material. The reaction was quenched with 50 mL saturated $NH_4Cl$ (aq). The layers were separated, and the aqueous layer was extracted with 2x 100 mL 90% EtOAc/hexanes. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. . Purification by flash chromatography over silica gel (20% to 50% EtOAc/ Hexanes) afforded 1.20 g (7.44 mmol, 99%) of thiazoldinethione **32** as a white crystalline solid. The desired product **33** was obtained as a very viscous colourless oil (3.180g, 6.93 mmol, 93% )This material was judged to be of >95 % purity by $^1$H NMR analysis as the diol could be separated from the minor diastereomer carried in from the previous reaction.

$R_f$ = 0.15 (30% EtOAc/hexanes, not UV active, stains blue in anisaldehyde)

$[\alpha]^{20}_D$ = -47.7 (*c* 1.52, $CHCl_3$);

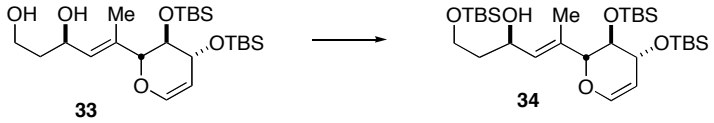
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.37 (d, *J* = 6.2, 1.0 Hz, 1 H), 5.56 (d, *J* = 8.5, 1.3 Hz, 1H), 4.69 (dd, *J* = 6.2, 0.3 Hz, 1H), 4.67- 4.63 (m, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 4.11 (t, *J* = 2.6 Hz, 1H), 3.86 (app. t, *J* = 4.7 Hz, 1H), 3.85- 3.77 (m, 2H), 2.40 (m, 1H), 1.97 (br. s, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.71 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.07 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ143.6, 133.5, 131.0, 102.9, 83.3, 71.7, 69.8, 68.6, 61.3, 38.8, 26.4, 26.1, 18.6, 18.4, 13.7, -3.4, -3.5, -3.6, -4.4;

IR(film) 3353.8, 2929.4, 2857.3, 1649.8, 1471.4, 1252.3, 1120.6, 835.7, 777.2 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{46}O_5Si_2$ $[M + Na]^+$ : 481.2776 ; found : 481.2766(ESI)

**(*R*,*E*)-5-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)-1-((*tert*-butyldimethylsilyl)oxy)hex-4-en-3-ol (34)**




Diol **33** (2.90g, 6.32 mmol) was dissolved in 32 mL $CH_2Cl_2$ under nitrogen. Triethylamine (1.77 mL, 12.6 mmol, 2.0 eq) was added. The resulting mixture was cooled to 0 °C. The septum was briefly removed and DMAP (77 mg, 0.63 mmol, 0.10 eq) and TBSCl (1.05g, 6.95mmol, 1.1 eq) were added. The ice bath was allowed to decay over 4 hours. The reaction was quenched by the addition of 1 mL MeOH, followed by dilution with 50 mL $CH_2Cl_2$. The organic layer was washed with 20 mL of water then washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% EtOAc/ Hexanes) afforded 3.160 g (5.51 mmol, 87%) of hydrogenation substrate **34** as a clear colourless oil which was judged to be >95% purity by $^1$H NMR. Flushing the column with 50% EtOAc/ hexanes yielded recovered diol **33** (137 mg, 0.299 mmol, 5 % ). A product attributed to protection of the secondary alcohol represented the balance of the material, unfortunately attempts to selectively deprotect this to regenerate diol **33** led to inconsequential recovery.

$R_f$ = 0.45 (10% EtOAc/hexanes, stains blue in CAM)

$[\alpha]^{20}_D$ = -43.6 (*c* 1.76, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 6.36 (d, *J* = 6.2 Hz, 1H), 5.54 (d, *J* = 8.2 Hz, 1H), 4.67 (dd, *J* = 6.2, 3.2 Hz, 1H), 4.64 – 4.58 (apt. septet, *J* = 3.9, 1H), 4.17 (d, *J* = 6.7 Hz, 1H),

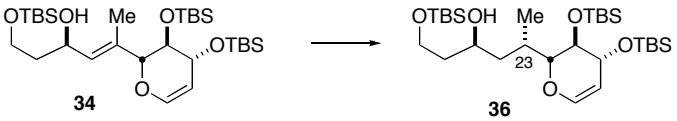
4.13 (apt. t, $J$ = 3.8 Hz, 1H), 3.90 - 3.83 (m, 2H), 3.80 – 3.75 (m, 1H), 1.78 – 1.69 (m, 2H), 1.69 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.07 (s, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 143.7, 132.5, 131.9, 102.9, 83.6, 71.8, 68.0, 61.8, 39.0, 26.4, 26.2 (2 signals), 26.1, 18.5, 18.4 (2 signals), 13.6, -3.4, -3.5, -3.6, -4.3, -5.2 (2 signals)

IR(film) 3510.7, 2955.5, 2858.4, 1652.3, 1472.6, 1388.8, 1361.9, 1254.6, 1093.1, 836.1, 776.7 $cm^{-1}$;

Exact Mass Calc. for $C_{29}H_{60}O_5Si_3$ $[M + Na]^+$ : 595.3641 ; found : 595.2642 (ESI)

**(3*S*,5*S*)-5-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)-1-((*tert*-butyldimethylsilyl)oxy)hexan-3-ol (36)**




A 25 mL scintillation vial equipped with the largest size stirbar that would fit was oven dried at 100 °C for 24 hours. The vial was transferred to a glovebox. Hydrogenation catalyst **55** (23 mg, 0.038 mmol, 0.02 eq) was loaded into the vial, which was then sealed with a suba® septum and removed from the glovebox. Separately, hydrogenation substrate **34** (1.10 g, 1.92 mmol, 1 eq) was dissolved in 5 mL $CH_2Cl_2$. The septum on the vial containing hydrogenation catalyst **55** was vented with a needle, and the solution of substrate was transferred to the vial using a syringe and needle to produce an orange solution. The septum was removed and the scintillation vial was transferred to a 40 mL stainless steel autoclave. The pressure head was screwed on the autoclave and the

autoclave was pressurized to 200 psig, then vented to 20 psig 3 times. The autoclave was pressurized to 200 psig a fourth time, then the pressure was reduced to 100 psig. After 1 hour, it was observed the pressure had decreased to 84 psig and remained static. The autoclave was vented, and the top removed to reveal a pale yellow solution. This solution was concentrated *in vacuo* and subsequently taken up in diethyl ether and filtered through Celite®, with several washings. The ether was removed *in vacuo* to give a pale yellow oil which was purified by flash chromatography over silica gel (3% EtOAc/ Hexanes) to afford 1.10g (1.91 mmol, 99% yield) of hydrogenation product **36** as a clear colourless oil.

$R_f$ = 0.50 (10% EtOAc/hexanes, stains violet in anisaldehyde)

$[\alpha]^{20}_D$ = -33.4 (*c* 3.33, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 6.0, 1.2 Hz, 1H), 4.64 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.21- 4.18 (m, 1H), 3.92- 3.88 (m, 1H), 3.87 (q, *J* = 5.1 Hz, 1H), 3.82- 3.79 (m, 1H), 3.78- 3.75 (m, 1H), 3.60 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.93 (d, *J* = 3.2 Hz, 1H), 2.42- 2.34 (m, 1H), 1.67- 1.63 (m, 2H), 1.63- 1.58 (m, 1H), 1.36 (ddd, *J* =13.3, 8.8, 4.1 Hz, 1H), 0.93 (d, *J* = 6.0, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 6H), 0.07 (s, 6H);

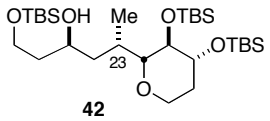
$^1$H NMR (600 MHz, $C_6D_6$) δ 6.27 (d, *J* = 6.1 Hz, 1H), 4.67 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.39- 4.37 (m, 1H), 4.00 (dd, *J* = 8.3, 5.5 Hz, 1H), 3.98- 3.93 (m, 1H), 3.85 (dd, *J* = 8.3, 3.3, 1H), 3.68- 3.64 (m, 1H), 3.61- 3.56 (m, 1H), 2.78- 2.70 (m, 1H), 2.68 (d, *J* = 3.2 Hz, 1H), 1.73 (ddd, *J* = 14.0, 9.8, 4.5 Hz, 1H), 1.62- 1.55 (m, 1H), 1.52 – 1.43 (m, 2H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.05 (s, 9H), 1.02 (s, 9H), 0.91 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H), 0.17 (s, 3H), -0.01 (s, 3H), -0.01 (s, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 143.6, 103.1, 82.3, 71.7, 71.4, 69.3, 62.3, 41.8, 39.3, 27.8, 26.3, 26.0, 25.9, 18.4, 18.2, 18.1, 13.6, -3.2, -3.4, -3.6, -4.6, -5.5 (2 signals);

IR(film) 3529.3, 2930.1, 2857.9, 1653.9, 1472.2, 1389.5, 1254.5, 1119.5, 1045.6, 836.2, 777.2 $cm^{-1}$;

Exact Mass Calc. for $C_{29}H_{62}O_5Si_3$ $[M + Na]^+$ : 597.3797 ; found : 597.3805 (ESI)

**Overhydrogenation Product (42)**




**42**

A 25 mL scintillation vial equipped with the largest size stirbar that would fit was oven dried at 100 °C for 24 hours. The vial was transferred to a glovebox. Crabtree's catalyst **40** (10.1 mg, 0.0126 mmol, 0.05 eq) was loaded into the vial, which was then sealed with a suba® septum and removed from the glovebox. Separately, hydrogenation substrate **34** (145 mg, 0.253 mmol, 1 eq) was dissolved in 2 mL $CH_2Cl_2$. The septum on the vial containing the Crabtree's catalyst **40** was vented with a needle, and the solution of substrate was transferred to the vial using a syringe and needle to produce a bright orange solution. The septum was removed and the scintillation vial was transferred to a 40 mL stainless steel autoclave. The pressure head was screwed on the autoclave and the autoclave was pressurized to 200 psig, then vented to 20 psig 3 times. The autoclave was pressurized to 200 psig a fourth time, then the pressure was reduced to 100 psig. After 70 minutes the bomb was vented and disassembled and the vial containing a straw yellow solution was removed. The solvent was removed *in vacuo* and the residue was taken up in diethyl ether and filtered through Celite®. The ether was removed *in vacuo* to give a pale

yellow oil which was purified by flash chromatography over silica gel (3% EtOAc/ Hexanes) to afford 10 mg of bicycle **58** (0.022 mmol, 9%) and 120 mg of a single diastereomer of overhydrogenation product **42** (0.209 mmol, 83%) as a clear colourless oil.

Characterization Data for the overhydrogenation product **42**:

$R_f$ = 0.40 (10% EtOAc/hexanes, not UV active, stains brown in anisaldehyde)

$[\alpha]^{20}_D$ = -8.8 (*c* 3.9, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 3.90 – 3.82 (m, 2H), 3.81 – 3.76 (m, 1H), 3.66 – 3.61 (m, 1H), 3.33 (t, *J* = 7.8 Hz, 1H), 3.32 – 3.29 (m, 1H), 2.99 (dd, *J* = 8.8, 1.8 Hz, 1H), 2.93 (d, *J* = 3.5, 1H), 2.22 (apt. septet, *J* = 6.6, 1H), 1.92 – 1.87 (m, 1H), 1.72 – 1.66 (m, 1H), 1.65 – 1.56 (m, 3H), 1.45 – 1.40 (m, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H), 0.07 (s, 3H);

$^1$H NMR (600 MHz, $C_6D_6$) δ 4.02- 3.95 (m, 1H), 3.70- 3.64 (m, 2H), 3.63- 3.57 (m, 2H), 3.50 (t, *J* = 8.8 Hz, 1H), 3.14 (ap. dd, *J* = 7.8, 1.0 Hz, 1H), 3.09 (ap. dd, *J* = 11.7, 1.5 Hz, 1H), 2.70 (d, *J* = 3.4 Hz, 1H), 2.61- 2.53 (m, 1H), 1.77 – 1.71 (m, 1H), 1.69- 1.61 (m, 2H), 1.61- 1.55 (m, 1H), 1.54- 1.47 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 9H), 0.97 (s, 9H), 0.90 (s, 9H), 0.27 (s, 3H), 0.21 (s, 3H), 0.13 (s, 3H), 0.05 (s, 3H), -0.02 (s, 6H)

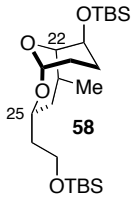
$^{13}$C NMR (100 MHz, $CDCl_3$) δ 84.0, 75.7, 73.9, 69.5, 65.0, 62.2, 42.6, 39.0, 35.4, 28.1, 26.5, 26.2, 25.8, 18.5, 18.2, 18.1, 13.2, -2.5, -2.8, -3.7, -4.4, -5.5(2 signals);

IR(film) 3528.8, 2955.4, 2857.2, 1463.1, 1388.0, 1255.3, 1113.3, 834.7, 776.6 $cm^{-1}$;

Exact Mass Calc. for $C_{29}H_{64}O_5Si_3$ $[M + H]^+$ : 577.4134 ; found : 577.4032 (ESI)

Characterization Data for the Bicycle **58**:

**Bicycle 58**




$R_f$ = 0.70 (10% EtOAc/hexanes, not UV active, stains light brown in anisaldehyde)

$[\alpha]^{20}_D$ = -18.7 (*c* 3.76, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 4.92 (d, *J* = 5.3 Hz, 1H), 4.27- 4.22 (m, 1H), 3.96- 3.91 (m, 1H), 3.70- 3.62 (m, 2H), 2.07- 1.99 (m, 1H), 1.96- 1.91 (m, 1H), 1.84- 1.79 (m, 1H), 1.69- 1.60 (m, 2H), 1.59- 1.47 (m, 3H), 1.39 (ap. q, *J* = 10.7 Hz, 1H), 0.95 (d, *J* = 9.3 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H);

$^1$H NMR (500 MHz, $CDCl_3$) δ 5.09 (d, *J* = 4.9 Hz, 1H), 4.37 (ap. pentet, *J* = 6.3 Hz, 1H), 4.09 (td, *J* = 10.2, 3.9 Hz, 1Hz), 3.88 (ap. t, *J* = 4.4 Hz, 1H), 3.79- 3.73 (m, 1H), 3.67- 3.63 (m, 1H), 2.04 (m, 1H), 1.83- 1.70 (m, 2H), 1.68 – 1.52 (m, 2H), 1.48- 1.32 (m, 2H), 1.09- 0.97 (m, 2H), 0.99 (s, 9H), 0.95 (s, 9H), 0.94 (d, peak occluded, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 94.8, 83.5, 70.5, 64.9, 59.7, 41.8, 39.4, 37.2, 27.9, 26.2, 25.9, 18.3, 18.0, 17.9, -3.2, -4.4, -5.3 (2 signals)

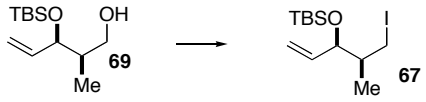
IR(film) 2955.6, 2857.5, 1462.7, 1255.4, 1132.6, 1087.5, 836.7, 773.9 $cm^{-1}$;

Exact Mass Calc. for $C_{23}H_{48}O_4Si_2$ $[M + H]^+$ : 445.3164 ; found : 445.3156 (ESI)

Alternative Overhydrogenation:

The above reaction was conducted with clean, diastereomerically pure hydrogenated substrate **36** (167 mg, 0.290 mmol) as the substrate and **40** as the catalyst. The substrate was exposed to 100 psi of hydrogen for 35 minutes. The work-up was as above. Purification with 2% EtOAc/hexanes yielded 78 mg ( 0.175 mmol, 60%) of Bicycle **58** with characterization data in accordance with that given above. Overhydrogenation product **42** was also obtained. The factors controlling the ratio of the two products are not understood, as this reaction gave a varying yield of Bicycle **58** from 10% to 40% over 3 attempts, with efforts made to reproduce the above conditions.

***tert*-butyl(((3*R*,4*S*)-5-iodo-4-methylpent-1-en-3-yl)oxy)dimethylsilane (67)**



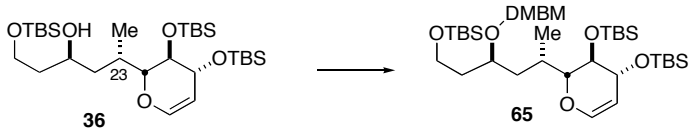

Triphenylphosphine (5.46 g, 20.8 mmol, 1.2 eq) and imidazole (1.48 g, 21.7 mmol, 1.25 eq) were dissolved in 60 mL $CH_2Cl_2$ and cooled to 0 ºC. To the stirring solution was added iodine (5.29 g, 20.8 mmol, 1.2 eq) and the resulting yellow suspension was stirred for 25 minutes. Alcohol **69** (4.01 g, 17.4 mmol, 1 eq) was dissolved in 10 + 5 mL $CH_2Cl_2$ and added dropwise. The cooling bath was removed. The reaction was stirred for 4 hours, until 2 D TLC (20% EtOAc/hexanes, Anisaldehyde) showed completion of the reaction. It should be noted that formation of the activated phosphonium and complete consumption of alcohol **69** is rapid. Conversion of the activated intermediate to iodide **67**

is slow. When conversion of the activated intermediate to the iodide is complete, the baseline no longer contains a blue spot, and 2 D TLC no longer shows streaking.

The reaction is concentrated *in vacuo* and the residue is purified by flash chromatography (1 % $Et_2O$ in pentane) to afford 4.30 g (12.6 mmol, 73 %) of iodide **67** as a clear colourless oil.

Rf = 0.95 (20% EtOAc/hexanes, faintly UV active, stains blue in Anisaldehyde)

**(*S*)-5-((*S*)-2-((2*R*,3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)propyl)-1-(3,4-dimethoxyphenyl)-9,9,10,10-tetramethyl-2,4,8-trioxa-9-silaundecane (65)**




((3,4-dimethoxybenzyloxy)methyl)(methyl)sulfane (1.20 g, 5.27 mmol, 1.7 eq) was dissolved in 5.27 mL $CH_2Cl_2$. The pale yellow solution was cooled to -78 °C. To this solution was added $SO_2Cl_2$ (1.0 M solution in $CH_2Cl_2$, 5.72 mL, 5.72 mmol, 1.87 eq). The resulting dark yellow solution was stirred at -78 °C for one hour, then the cooling bath was removed and the solution was stirred at ambient temperature for one hour. The solution was concentrated *in vacuo* on a rotavap within a fumehood, with no external heating. The resulting crude DMBM chloride was stirred under vacuum for 20 minutes. Meanwhile, TBAI (67mg, 0.263 mmol, 0.086 eq) was dissolved in 0.5 ml $CH_2Cl_2$ in a 50 mL flame dried Schlenk tube under nitrogen. Hydrogenation product **36** (1.78g, 3.1 mmol) in 1 mL $CH_2Cl_2$ was added using a needle and syringe, and the flask was rinsed with a further 3 x 1mL $CH_2Cl_2$. Freshly distilled Hunig's base (1.41 mL, 7.90 mmol, 2.6 eq) was added. The crude DMBMCl was dissolved in 1 mL of $CH_2Cl_2$ and transferred to

the Schlenk flask, and 2 x 1 mL of $CH_2Cl_2$ were used to quantitate the transfer. The resulting golden yellow solution was lowered into a preheated 40 °C oil bath and the Schlenk tube was allowed to thermally equilibrate and then was sealed. The reaction was protected from light and stirred for 23 hours. After 23 hours, the bright orange reaction mixture was quenched by dilution with 20 mL $CH_2Cl_2$ and the addition of 4 mL saturated $NaHCO_3$ (aq). The mixture was transferred to a separatory funnel, an additional 20 mL of water was added and the layers were separated. The aqueous layer was washed with 4x 20 mL of $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% –> 10% EtOAc/ Hexanes) afforded 2.20 g (2.94 mmol, 95 %) of DMBM ether **65** as a clear colourless oil which was judged to be >95% purity by $^1$H NMR.

$R_f$ = 0.45 (10% EtOAc/hexanes, faintly UV active, stains purple in CAM)

$[\alpha]^{20}_D$ = -25.0 (*c* 2.85, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.28 (d, *J* = 6.0 Hz, 1H), 4.78 (AB d, *J* = 7.0 Hz, 1H), 4.73 (AB d, *J* = 7.0 Hz, 1H), 4.64 (dd, *J* = 5.9, 2.7 Hz, 1H), 4.57- 4.51 (m, 2H), 4.25- 4.22 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.87- 3.82 (m, 1H), 3.74- 3.70 (m, 3H), 3.57 (dd, *J* = 8.8, 3.1 Hz, 1H), 2.36- 3.29 (m, 1H), 1.87- 1.79 (m, 1H), 1.78- 1.67 (m, 2H), 1.50 (ddd, *J* = 13.8, 8.7, 5.0 Hz, 1H), 0.93- 0.91 (m, 12H), 0.88 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.11 (br. s, 9H), 0.03 (s, 3H), 0.03 (s, 3H);

$^1$H NMR (600 MHz, $C_6D_6$) δ 6.97 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.24 (dd, *J* = 6.2, 1.0 Hz, 1H), 4.91 (AB d, *J* = 6.9 Hz, 1H), 4.86 (AB d, *J* = 6.9 Hz, 1H), 4.72- 4.64 (m, 3H), 4.41- 4.39 (m, 1H), 4.10- 4.05 (m, 1H), 3.95 (dd,

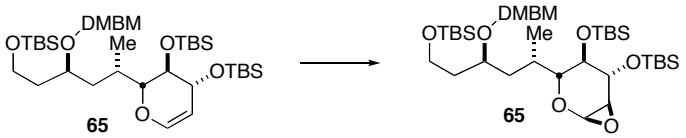
*J* = 8.9, 5.9 Hz, 1H), 3.82- 3.78 (m, 2H), 3.76- 3.72 (m, 1H), 3.47 (s, 3H), 3.40 (s, 3H), 2.65- 2.57 (m, 1H), 2.04- 1.94 (m, 2H), 1.91- 1.83 (m, 1H), 1.74 (ddd, *J* = 13.8, 8.8, 4.9 Hz, 1H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.03 (s, 9H), 1.01 (s, 9H), 0.98 (s, 9H), 0.27 (s, 3H), 0.20 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.07 (s, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.0, 148.5, 143.8, 130.6, 120.4, 111.2, 110.9, 103.4, 93.8, 81.9, 73.5, 72.1, 71.9, 69.5, 59.7, 55.9, 55.8, 39.4, 38.2, 27.8, 26.4, 26.0, 25.9, 18.4, 18.1 (2 signals), 13.3, -3.0, -3.2, -3.5, -4.7, -5.4;

IR(film) 2930.1, 1857.1, 1651.3, 1517.3, 1463.6, 1255.5, 1104.3, 1036.2, 836.1, 777.0 $cm^{-1}$;

Exact Mass Calc. for $C_{39}H_{74}O_8Si_3$ $[M + Na]^+$ : 777.4584 ; found : 777.4583 (ESI)

**DMDO oxidation (66)**




Glycal **65** (1.19g, 1.58 mmol, 1 eq) was dissolved in 20 mL $CH_2Cl_2$ and cooled to 0 °C. DMDO in acetone, that was stood over solid $K_2CO_3$ at -20 °C for 24 hours, but not dried in any other way (20 mL, an excess) was added dropwise using a glass pipette. Use of DMDO that is stood over $K_2CO_3$ is required to avoid decomposition, but exhaustive drying is not necessary, and is wasteful of DMDO solution. After 1 hour, TLC (20% EtOAc/hex, anisaldehyde, product decomposes on TLC plate) showed that the starting material was consumed. The volatiles were removed *in vacuo* and the residue was taken up in 10 mL benzene. Any droplets of water were removed using a pipette. The benzene

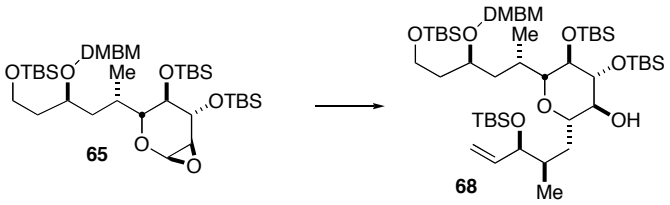
was removed, and the azeotroping was repeated twice more. The resulting clear colourless oil **66** was used without any further purification in the next step.

Partial Characterization:

$R_f$ = 0.10, 0.20 (two spots, not UV active, stain brown in Anisaldehyde)

$^1$H NMR (600 MHz, $CDCl_3$) δ

**Fragment Coupling Product (68)**




Magnesium turnings (460 mg, 18.9 mmol, 1.5 eq. relative to 1,2 dibromoethane) were placed in a 2 neck flask equipped with a condenser, under argon. To the flask are added 12 mL $Et_2O$ and 6 mL toluene. 1,2 Dibromoethane (1.09 mL, 12.5 mmol) was added dropwise at such a rate that the vigorous reflux did not overwhelm the condenser. The resulting approximately 0.7 M solution of $MgBr_2$ was used directly in the next step.

A freshly titrated solution of *t*BuLi in pentanes (1.63 M, 5.81 mL, 9.48 mmol, 6.0 eq) was was placed in a 100 mL RBF, equipped with a thermocouple to measure the internal temperature, under argon. The flask was cooled to -78 °C A solution of iodide **67** (1.62g, 4.74 mmol, 3.0 eq) in 6 mL $Et_2O$ was swiftly added, and the internal temperature rose to -35 °C. A milky white precipate instantly formed. After 2 minutes, when the temperature had returned to below -70 °C, 6 mL of THF was added, followed by the $MgBr_2$ solution (6.8 mL, 4.5 mmol, 3.0 eq). After 5 minutes, $Li_2CuCl_4$ (0.1 M in $Et_2O$, 3.16 mL, 0.316 mmol, 0.2 eq) is added and the solution is warmed to an internal temperature of -54 °C for 20 minutes. The resulting light brown suspension is cooled back to -78 °C. The

epoxide **66** is dissolved in 4 mL of THF, and this is added dropwise to the cuprate reaction. An additional 2 mL of THF are used to quantitate the reaction. After 30 minutes, the reaction is removed from the cooling bath. After an additional half hour of stirring the orange solution is quenched with 5 mL of a 1:1 mixture of saturated $NH_4Cl_{(aq)}$ and 28- 30 % $NH_{3(aq)}$ and stirred for 5 minutes. The resulting mixture is transferred to a separatory funnel and diluted with 100 mL of a 90% EtOAc/hexanes mixture and 20 mL of water. The layers are separated and the aqueous layer is washed with 2 x 50 mL of 90% EtOAc/hexanes. The organic layers are washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography over silica gel (5% EtOAc/ Hexanes) afforded 1.24 g of coupling product **68** (1.26 mmol, 80% over 2 steps) as a clear colourless oil which was judged to be >95% purity by $^1$H NMR.

$R_f$ = 0.70 (20% EtOAc/hexanes, faintly UV active, stains purple in anisaldehyde)

$[\alpha]^{20}_D$ = +7.30 (*c* 2.91, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.89 (ap. d, *J* = 9.2 Hz, 1H), 6.83 (ap. d, *J* = 8.5 Hz, 1H), 5.81 (ddd, *J* =16.8, 10.4, 6.3 Hz, 1H), 5.14 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.07 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.01 (dd, *J* = 6.3, 4.1 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.84 (ap. pent., *J* = 6.1 Hz, 1H), 3.74- 3.67 (m, 2H), 3.57 (t, *J* = 7.3 Hz, 1H), 3.55 (t, *J* = 7.6 Hz, 1H), 3.19 (td, *J* = 8.5, 3.1 Hz, 1H), 3.15- 3.11 (m, 1H), 3.06 (dd, *J* = 10.2, 2.1 Hz, 1H), 2.15 (ap. sext. *J* =7.0 Hz, 1H), 1.97 (ddd, *J* = 14.1, 6.2, 3.1 Hz, 1H), 1.93 (d, *J* = 5.1 Hz, 1H), 1.90 (pent., *J* = 6.7 Hz, 1H), 1.81- 1.76 (m, 1H), 1.73 (ap. sext., *J* = 6.6 Hz, 1H), 1.58 (t, *J* =7.4 Hz, 1H), 1.17 (ddd, *J* = 9.1, 8.9, 7.3 Hz, 1H), 0.93- 0.91 (m, 12H), 0.90 (s, 9H), 0.90 (s, 9H), 0.89- 0.88 (m, 12H), 0.15 (s, 6H), 0.14 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H);

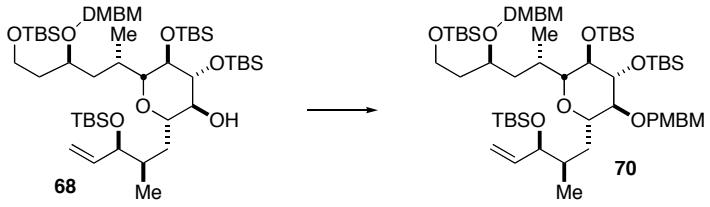
$^{1}$H NMR (600 MHz, $C_6D_6$) δ 6.99 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.91 (ddd, *J* = 16.8, 10.4, 6.3 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.08 (dt, *J* = 0.8, 10.6 Hz, 1H), 4.94 (d, *J* = 6.7 Hz, 1H), 4.88 (d, *J* = 6.9 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.14- 4.14 (m, 1H), 4.10- 4.06 (m, 1H), 3.88- 3.84 (m, 1H), 3.83- 3.79 (m, 1H), 3.71 (t, *J* = 7.9 Hz, 1H), 3.66 (t, *J* = 8.7 Hz, 1H), 3.51 (s, 3H), 3.41 (s, 3H), 3.30 (td, *J* = 3.0, 9.0 Hz, 1H), 3.24 (dd, *J* = 8.8, 1.6 Hz, 1H), 3.20- 3.15 (m, 1H), 2.71- 2.41 (m, 1H), 2.18 (ddd, *J* = 14.0, 6.5, 2.9 Hz, 1H), 2.10 (ap. sext., *J* = 6.3 Hz, 1H), 2.06- 2.01 (m, 1H), 1.94- 1.86 (m, 2H), 1.86- 1.80 (m, 1H), 1.65 (d, *J* = 5.1 Hz, 1H), 1.32- 1.26 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 9H), 1.05 (s, 9H), 1.04 (s, 9H), 1.01 (s, 9H), 0.28 (s, 3H), 0.27 (s, 3H), 0.25 (s, 3H), 0.21 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.0, 148.5, 140.2, 130.6, 120.3, 114.6, 111.1, 110.9, 93.6, 83.9, 80.5, 78.9, 76.6, 75.9, 73.4, 73.3, 69.4, 59.7, 55.9, 55.8, 40.5, 38.5, 37.0, 35.7, 29.1, 26.4, 26.2, 25.9, 18.6, 18.2 (2 signals), 16.0, 12.9, -2.3 (2 signals), -2.9, -3.4, -4.1, -4.8, -5.4;

IR(film) 3532.1, 2954.7, 2893.9, 2856.6, 1728.0, 1594.3, 1517.2, 1471.8, 1387.7, 1360.7, 1255.5, 1093.1, 1033.6, 938.4, 837.0, 775.2, 671.6 $cm^{-1}$;

Exact Mass Calc. for $C_{51}H_{100}O_{10}Si_4$ $[M + Na]^+$ : 1007.6285 ; found : 1007.6272 (ESI)

**PMBM Ether (70)**




((4-methoxybenzyloxy)methyl)(methyl)sulfane, (1.41 g, 7.10 mmol, 5 eq) was dissolved in 7.10 mL $CH_2Cl_2$. The pale yellow solution was cooled to -78 °C. To this solution was added $SO_2Cl_2$ (1.0 M solution in $CH_2Cl_2$, 7.10 mL, 7.10 mmol, 5 eq). The resulting dark yellow solution was stirred at -78 C for one hour, then the cooling bath was removed and the solution was stirred at ambient temperature for one hour. The solution was concentrated *in vacuo* on a rotavap within a fumehood, with no external heating. The resulting crude PMBM chloride was stirred under vacuum for 20 minutes. Meanwhile, TBAI (36 mg, 0.142 mmol, 0.10 eq) was dissolved in 0.5 ml $CH_2Cl_2$ in a 50 mL flame dried Schlenk tube under nitrogen. Fragment coupling product **68** (1.40 g, 1.42 mmol) in 1 mL $CH_2Cl_2$ was added using a needle and syringe, and the flask was rinsed with a further 3 x 1mL $CH_2Cl_2$. Freshly distilled Hunig's base (2.5 mL, 14.2 mmol, 10 eq) was added. The crude PMBMCl was dissolved in 1 mL of $CH_2Cl_2$ and transferred to the Schlenk flask, and 2 x 1 mL of $CH_2Cl_2$ were used to quantitate the transfer. The resulting pinkish solution was lowered into a preheated 40 °C oil bath and the Schlenk tube was allowed to thermally equilibrate and then was sealed. The reaction was protected from light and stirred for 36 hours. After 36 hours, the reaction was poured on a column, prequilibrated 5% NEt3 in 50% EtOAc/hexanes. The material is eluted with more of the same eluent, and the product containing fractions are concentrated *in vacuo* to yield a brown oil. Purification by flash chromatography over silica gel (5% –> 10% EtOAc/ Hexanes) afforded 1.53 g of PMBM ether **70** as a clear colourless oil (1.35 mmol, 95 %) which was judged to be >95% purity by $^1$H NMR. Quenching the reaction with saturated $NaHCO_{3(aq)}$ followed by a standard aqueous extraction results in large quantities of what

is believed to be the paramethoxybenzyl acetal of formaldehyde ($R_f$ = 0.55 in 20% EtOAc/hexanes, UV active, stains bright pink in CAM) which is stubbornly inseparable from the desired product (though not detrimental to the subsequent ozonolysis/phosphonate addition reaction, after which it is readily separable).

Rf = 0.65 (20% EtOAc/hexanes, faintly UV active, stains blue/purple in CAM)

$[\alpha]^{20}_D$ = -8.5 (*c* 2.52, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.6 Hz, 2H), 6.89- 6.86 (m, 4H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.79 (ddd, *J* = 16.8, 10.4, 6.3 Hz, 1H), 5.10 (dt, *J* = 17.2, 1.7 Hz, 1H), 5.02 (dt, *J* = 10.4, 1.0 Hz, 1H), 4.81 (d, *J* =6.9 Hz, 1H), 4.79 (d, *J* = 8.2 Hz, 1H), 4.71 (d, *J* = 7.1 Hz, 1H), 4.68 (d, *J* =6.9 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.01- 3.99 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.87- 3.84 (m, 1H), 3.81 (s, 3H), 3.73- 3.67 (m, 2H), 3.67- 3.64 (m, 1H), 3.51- 3.47 (m, 1H), 3.38 (ap. t, *J* = 5.1 Hz, 1H), 3.15 (dd, *J* = 6.7, 3.2 Hz, 1H), 2.07- 2.01 (m, 1H), 1.92- 1.87 (m, 2H), 1.80- 1.69 (m, 2H), 1.66- 1.60 (m, 1H), 1.54- 1.49 (m, 1H), 1.38- 1.31 (m, 1H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.88 (s, 18H), 0.11 (s, 3H), 0.10 (s, 6H) 0.08 (s, 3H, 0.03 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H);

$^1$H NMR (600 MHz, $C_6D_6$) δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.97 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.69 (ddd, *J* = 17.0, 10.3, 6.2 Hz, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 5.01 (d, *J* = 6.7 Hz, 1H), 4.95 (d, *J* = 6.9 Hz, 1H), 4.87 (d, *J* = 6.9 Hz, 1H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.22- 4.19 (m, 1H), 4.15- 4.10 (m, 1H), 4.07 (t, *J* = 4.4 Hz, 1H), 3.90 (dd, *J* = 6.6, 6.0 Hz,

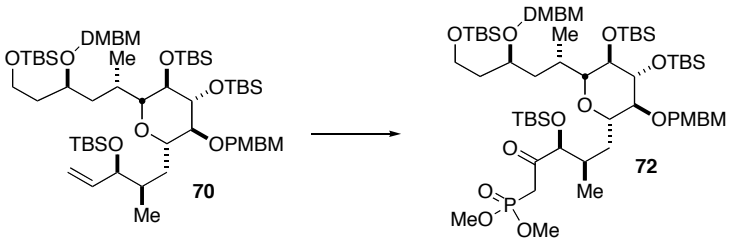
1H) 3.85- 3.77 (m, 2H), 3.66 (ap. t, *J* = 5.5 Hz, 1H), 3.51 (s, 3H), 3.51- 3.48 (m, 1H), 3.41 (s, 3H), 3.29 (s, 3H), 2.43- 2.37 (m, 1H), 2.26 (ddd, *J* = 13.6, 6.5, 3.1 Hz, 1H), 2.12- 2.05 (m, 2H), 1.98- 1.92 (m, 1H), 1.91- 1.86 (m, 1H), 1.82- 1.76 (m, 1H), 1.68- 1.62 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.08 (s, 9H), 1.04 (s, 18H), 1.00 (s, 9H), 0.27 (s, 3H), 0.25 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.18 (s, 3H), 0.13 (s, 3H), 0.10 (s, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) 159.1, 150.0, 148.5, 140.5, 130.6, 129.9, 129.3, 120.3, 114.4, 113.7, 111.1, 110.9, 93.7, 93.5, 84.2, 79.9, 78.2, 76.5, 75.9, 73.1, 72.9, 69.4, 69.2, 59.8, 55.9, 55.8, 55.2, 40.3, 38.5, 37.4, 37.3, 26.1, 26.0, 25.9, 18.2, 18.0 (2 signals), 15.8, 13.3, -3.1, -3.7 (2 signals), -4.0, -4.1, -4.7, -5.3; δ

IR(film) 2954.0, 2856.5, 1612.2, 1515.4, 1463.5, 1387.7, 1250.8, 1097.0, 1034.8, 836.5, 774.4 $cm^{-1}$;

Exact Mass Calc. for $C_{60}H_{110}O_{12}Si_4$ $[M + Na]^+$ : 1157.6966 ; found : 1157.6970 (ESI)

**Pyran Keto-Phosphonate (72)**




Alkene **70** (900 mg, 0.792 mmol, 1 eq) was dissolved in 20 mL $CH_2Cl_2$ and 2 mL pyridine was added. A pipette tip of Sudan III indicator was added. The reaction was cooled to -78 °C for 10 minutes with stirring to ensure it was thermally equilibrated. Ozone was sparged through until the colour faded from red to peachy orange. The reaction was then sparged with nitrogen for one minute. Triphenylphosphine (415 mg,

0.546 mmol, 2 eq) was added and the cooling bath was removed. After 50 minutes the solvent was removed *in vacuo* and the residue was employed directly in the next step.

TLC data for intermediate aldehyde:

$R_f$ = 0.60 (20% EtOAc/hexanes, faintly UV active, stains purple/blue in CAM)

Dimethyl methyl phosphonate (0.490 mL, 4.75 mmol, 6 eq) was dissolved in 10 mL THF under nitrogen and cooled to -78 °C. To the stirring reaction was added 2.94 M n-BuLi in hexanes (0.81 mL, 2.38 mmol, 3 eq) and the reaction was stirred for one hour. The aldehyde/ triphenylphosphine/ triphenylphosphine oxide mixture was dissolved in 5 mL THF and added dropwise to the phosphonate mixture. Another 3 + 2 mL of THF was used to quantitate the transfer. The reaction was stirred for 40 minutes at -78 °C until TLC (30% EtOAc/hexanes, CAM) showed consumption of starting material. The reaction was quenched with $NH_4Cl_{(aq)}$ and diluted with 50 mL 90% EtOAc/hexanes. An emulsion typically results from this reaction, so shaking is done gently. The reaction mixture was washed with brine, then dried over $Na_2SO_4$ solvent was removed *in vacuo*. Flash chromatography (20% to 50% EtOAc/hexanes) afforded 800 mg (0.635 mmol, 80% over 2 steps) of an inconsequential mixture of diastereomers that was used directly in the next step.

TLC data for intermediate alcohols:

$R_f$= 0.30 (50 % EtOAc/hexanes, faintly UV active, stains purple in CAM)

This residue dissolved in 15 mL $CH_2Cl_2$ and Dess-Martin periodinane (348 mg, 0.826 mmol, 1.3 eq) was added. TLC after 1 hour showed complete conversion to pyran beta ketoester **72**. The reaction was diluted with 15 mL $CH_2Cl_2$, 3 mL hexanes and cooled to 0 °C. 6 mL saturated $NaS_2O_{3(aq)}$ and 6 mL saturated $NaHCO_{3(aq)}$ were added and the

biphasic reaction mixture was stirred until the layers became clear. The layers were separated, the aqueous layer was extracted with 60 mL 90% EtOAc/hexanes and the combined organic layers were washed with saturated $NaHCO_{3(aq)}$, brine, then dried over $Na_2SO_4$. Concentration of the residue *in vacuo* yielded a tacky solid that was purified by flash chromatography on silica (30% EtOAc/hexanes) to yield 795 mg Pyran phosphonate (0.632 mmol, 79% over 3 steps) as a clear colourless oil.

$R_f$ = 0.45 (50 % EtOAc/hexanes, UV active, stains purple in CAM)

$[\alpha]^{20}_D$ = -1.0 (*c* 2.49, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.70 Hz, 2H), 6.89- 6.86 (m, 4H), 6.82 (d, *J* = 7.90 Hz, 1H), 4.81 (d, *J* = 9.5 Hz, 1H), 4.80 (d, *J* = 9.6 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* =11.4 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.14 (d, *J* = 3.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 (ap. t, *J* = 3.8 Hz, 1H), 3.80 (s, 3H), 3.77 (br. s, 3H), 3.75 (br. s, 3H), 3.72- 3.67 (m, 3H), 3.49 (ddd, *J* = 10.2, 6.3, 3.2 Hz, 1H), 3.39 (dd, *J* = 5.6, 4.4 Hz, 1H), 3.21- 3.14 (m, 2H), 3.02 (dd, *J* = 21.5, 15.5 Hz, 1H), 2.20- 2.14 (m, 1H), 2.09- 2.01 (m, 1H), 1.94- 1.84 (m, 2H), 1.75- 1.70 (m, 1H), 1.68- 1.62 (m, 1H), 1.51- 1.43 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88- 0.87 (m, 12H), 0.11 (s, 3H), 0.10 (s, 6H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03- 0.02 (m, 9H);

$^1$H NMR (600 MHz, $C_6D_6$) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.00 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 6.86- 6.83 (m, 3H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.98 (d, *J* = 6.8 Hz, 1H), 4.90 (d, *J* = 6.9 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 3.2 Hz, 1H), 4.19- 4.13 (m, 1H), 4.08 (t, *J* = 4.4 Hz, 1H), 3.92 (dd, *J* = 5.7, 4.4 Hz, 1H), 3.90 -

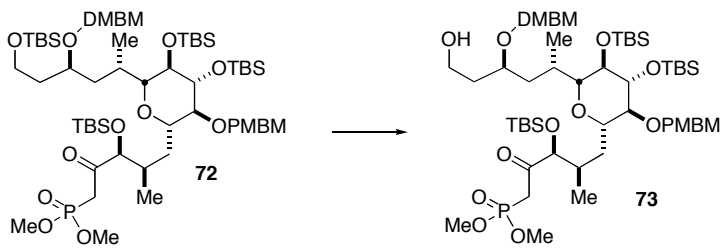
3.81 (m, 3H), 3.67 (dd, *J* = 6.0, 4.5 Hz, 1H), 3.56 (dd, *J* = 6.3, 3.8 Hz, 1H), 3.52 (s, 3H), 3.52 (d, *J* = 11.1 Hz, 3H), 3.47 (d, *J* = 11.2 Hz, 3H), 3.41 (s, 3H), 3.31 (s, 3H), 3.28- 3.20 (m, 1H), 2.93 (dd, *J* = 14.6, 22.1 Hz, 1H), 2.51- 2.45 (m, 1H), 2.45- 2.39 (m, 1H), 2.24 (ddd, *J* = 13.9, 8.2, 3.9 Hz, 1H), 2.14 (ap. sext., *J* = 7.5 Hz, 1H), 1.99 (ddd, *J* = 13.3, 8.9, 3.6 Hz, 1H), 1.95 (ap. sext., *J* = 7.5 Hz, 1H), 1.81 (ddd, *J* = 13.6 9.9, 3.7Hz, 1H), 1.75 (ddd, *J* = 15.0, 11.2, 5.7 Hz, 1H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.08- 1.07 (m, 12H), 1.06 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.20 (s, 3H), 0.10 (s, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.7 (d, *J* = 7.4 Hz), 159.1, 148.9, 148.5, 130.6, 129.8, 129.2, 120.2, 113.7, 111.0, 110.9, 110.3, 93.7, 93.5, 84.8, 80.6 (2 signals), 80.1, 76.7, 75.4, 73.1, 72.7, 69.4, 69.2, 59.8, 55.9, 55.8, 55.7, 55.2, 52.8 (2 signals), 52.7, 40.1, 38.4, 38.0, 36.7, 35.6, 33.7, 31.1, 29.6, 26.1, 25.9 (2 signals), 25.8, 18.2, 18.1, 18.0, 14.9, 13.7, -3.2, -3.8, -3.9, -4.1, -4.7, -5.0, -5.4;

IR(film) 2930.3, 2856.1, 1727.4, 1612.6, 1515.3, 1463.5, 1387.5, 1255.2, 1093.0, 1031.1, 939.7, 837.1, 776.1, 669.2 $cm^{-1}$;

Exact Mass Calc. for $C_{62}H_{115}O_{16}PSi_4$ $[M + Na]^+$ : 1281.6892 ; found : 1281.6922 (ESI)

**Elaborated Pyran Ketophosphonate (73)**



Pyran ketophosphonate **72** (201 mg, 0.160 mmol, 1 eq) was dissolved in a mixture of 3 mL MeOH and 3 mL $CH_2Cl_2$ and cooled to 0 °C. To the stirring mixture under air was added 4 mg (0.016 mmol, 0.1 eq) camphorsulfonic acid. After 1 hour, TLC (50% EtOAc/hexanes, CAM) showed complete consumption of starting material, so the reaction was quenched by the addition of 1 mL saturated $NaHCO_{3(aq)}$. The mixture was diluted with 50 mL 90% EtOAc/hexanes and the organic layer was separated. The organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. The polar phosphonate alcohol was held under high vacuum to remove all methanol which would interfere with the next step, but no other purification was required.

Characterization Data:

$R_f$ = Baseline (50% EtOAc/hexanes, UV active, stains purple in CAM)

$[\alpha]^{20}_D$ = +8.70 (*c* 1.45, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.90- 6.86 (m, 4H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.82 (dd, *J* = 6.9, 1.6 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.23 (d, *J* = 2.5 Hz, 1H), 3.94- 3.89 (m, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.83 (ap. t, *J* = 4.1 Hz, 1H), 3.80 (s, 3H), 3.79 (d, *J* = 6.9 Hz, 3H), 3.77 (d, *J* = 6.9 Hz, 3H), 3.77- 3.74 (m, 2H), 3.72 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.65 (dd, *J* = 6.9, 3.9 Hz, 1H), 3.53- 3.49 (m, 1H), 3.39 (ap. t, *J* = 5.0 Hz, 1H), 3.22 (dd, *J* = 6.9, 2.8 Hz, 1H), 3.17 (dd, *J* = 20.4, 15.7 Hz, 1H), 2.99 (dd, *J* = 21.9, 15.5 Hz, 1H), 2.28- 2.21 (m, 1H), 2.09- 2.03 (m, 1H), 1.91- 1.82 (m, 3H), 1.79- 1.69 (m, 2H), 1.61- 1.50 (m, 2H), 0.93 (d, *J* = 7.9 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 18H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H);

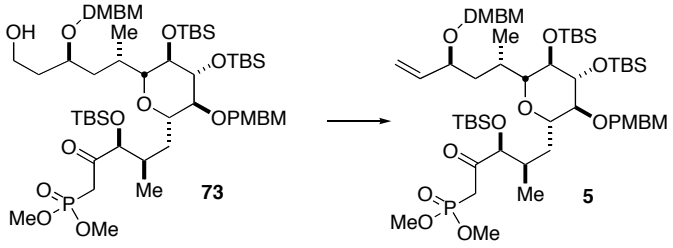
$^{1}$H NMR (600 MHz, $C_6D_6$) δ 7.35 (d, *J* = 8.6 Hz, 2H), 6.99- 6.97 (m, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 7.9 Hz, 1H), 5.04 (d, *J* = 6.8 Hz, 1H), 4.94 (d, *J* = 6.7 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.58 (s, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.18-4.14 (m, 1H), 4.06 (ap. t, *J* = 4.8 Hz, 1H), 3.93 (ap. t, *J* = 6.3 Hz, 1H), 3.86 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.82- 3.79 (m, 1H), 3.68 (ap. t, *J* = 5.6 Hz, 1H), 3.54 (dd, *J* = 7.5, 2.3 Hz, 1H), 3.52 (s, 3H), 3.46 (d, *J* = 11.1 Hz, 3H), 3.40 (s, 3H), 3.38 (d, *J* = 11.3 Hz, 3H), 3.29 (s, 3H), 3.17 (dd, *J* = 20.4, 14.4 Hz, 1H), 2.74 (dd, *J* = 22.7, 14.8 Hz, 1H), 2.52- 2.46 (m, 1H), 2.46- 2.41 (m, 1H), 2.19 (ddd, *J* = 13.5, 10.1, 2.8 Hz, 1H), 2.15- 2.05 (m, 2H), 2.05-1.99 (m, 1H), 1.95- 1.89 (m, 1H), 1.80 (ddd, *J* = 15.0, 11.1, 4.0 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.07 (s, 9H) 1.07 (s, 9H), 1.03 (s, 9H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.25 (s, 3H), 0.22 (s, 3H), 0.19 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.5, 159.1, 148.9, 148.6, 130.2, 129.7, 129.1, 120.3, 113.7, 111.1, 110.9, 93.9, 93.7, 84.2, 79.7, 79.5 (2 signals), 76.3, 75.7, 74.1, 72.8, 69.7, 69.2, 59.2, 55.8, 55.7, 55.1, 52.9 (2 signals), 52.8, 40.8, 38.1, 37.8, 36.6, 35.5, 32.5, 30.4, 29.6, 26.1, 25.9, 25.8, 18.2, 18.0, 17.9, 14.7, 13.1, -3.1, -3.8 (2 signals), -4.1, -4.6, -5.1;

IR(film) 3442.2, 2954.0, 2856.5, 1728.1, 1613.3, 1515.5, 1463.6, 1385.5, 1251.5, 1098.3, 1032.7, 837.5, 776.3, 666.90 $cm^{-1}$;

Exact Mass Calc. for $C_{56}H_{101}O_{16}PSi_3$ $[M + Na]^+$ : 1167.6021 ; found : 1167.6026 (ESI)

**Elaborate Pyran Ketophosphonate (5)**




To the residue of **73** was added *o*-nitrophenylselenocyanate (109 mg, 0.477 mmol, 3 theoretical equivalents) and the mixture was dissolved in 4 mL of THF under nitrogen. To the light brown solution was added $PBu_3$ (0.119 mL, 0.477 mmol, 3 theoretical equivalents) which resulted in the formation of a dark brown solution. This was allowed to stir for 1 hour, at which time TLC showed complete consumption of the starting material. To the brown mixture was added 4 mL of 30% $H_2O_2$ and the resulting biphasic mixture was stirred for 12 hours. TLC during this time shows oxidation to the selenoxide ($R_f$ = 0, stains dark purple) followed by formation of the Elaborated Pyran Ketophosphonate **5** ($R_f$ = 0.60 in 50% EtOAc/hexanes). The reaction is judged complete when no more material that stains blue is present on the baseline of the TLC. The reaction is diluted with 50 mL 90% EtOAc/hexanes and washed with saturated $NaHSO_3$ until the washings were neutral to KI/$KIO_3$/Starch peroxide test strips. This was washed with brine and dried over $Na_2SO_4$. Concentration *in vacuo* yielded a vile smelling orange residue which was purified by flash chromatography to yield 145 mg elaborate β–ketophosphonate (0.129 mmol, 81 %) as a dark yellow coloured oil that was > 95% pure by $^1$H NMR. Judging from the colour and the odour, selenium containing byproducts were present, which were not removed by chromatography. These do not appear to be detrimental to the next step.

$R_f$ = 0.60 (50% EtOAc/hexanes, UV active, stains blue-black in CAM)

$[\alpha]^{20}_{D}$ –20.3 (c = 3.21, $CHCl_3$);

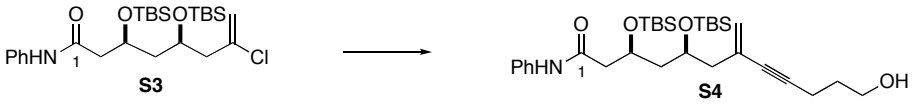
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.6 Hz, 2H), 6.89- 6.86 (m, 4H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.73 (ddd, *J* = 17.7, 10.4, 7.7 Hz, 1H), 5.23 (dd, *J* = 17.7, 0.7 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 4.6 Hz, 1H), 4.60 (d, *J* = 4.7 Hz, 1H), 4.47 (d, *J* = 16.3 Hz, 1H), 4.45 (d, *J* = 16.0 Hz, 1H), 4.23- 4.19 (m, 1H), 4.19 (d, *J* = 2.9 Hz, 1H), 3.88 (s, 3H) 3.87 (s, 3H), 3.83 (t, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 1.2 Hz, 3H), 3.76 (d, *J* = 1.3 Hz, 3H), 3.71- 3.69 (m, 1H), 3.51 (ddd, *J* = 9.5, 6.2, 3.0 Hz, 1H), 3.39 (dd, *J* = 5.7, 4.1 Hz, 1H), 3.22 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.15 (dd, *J* = 20.6, 10.5 Hz, 1H), 3.01 Hz, (dd, *J* = 21.6, 15.5 Hz, 1H), 2.22- 2.14 (m, 2H), 1.87 (qd, *J* = 7.0, 2.0 Hz, 1H), 1.75 (ddd, *J* = 13.6, 10.0, 3.4 Hz, 1H), 1.51- 1.45 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.5, 159.1, 149.0, 148.6, 139.0, 130.9, 130.5, 129.8, 129.2, 120.4, 117.0, 113.7, 111.1, 110.9, 93.8, 91.7, 84.8, 80.2 (2 signals), 80.1, 76.4, 75.6, 75.2, 72.7, 69.5, 69.2, 55.9, 55.8, 55.2, 52.8 (broad signal), 41.0, 38.0, 36.8, 35.7, 33.2, 30.8, 29.6, 26.1, 26.0, 25.8, 18.2, 18.0 (2 signals), 14.9, 13.4, -3.1, -3.8, -3.9, -4.0, -4.6, -5.0;

IR (film) 2954.6, 2856.4, 1727.8, 1612.8, 1515.5, 1463.7, 1252.4, 1098.8, 1032.9, 837.7, 776.6;

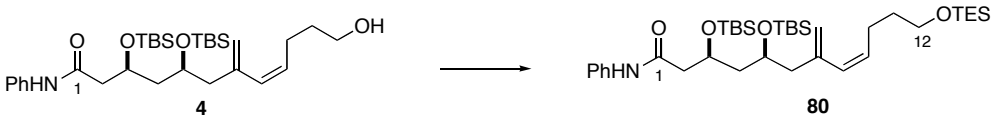
Exact Mass Calc. for $C_{56}H_{99}O_{15}PSi_3$ $[M + Na]^+$ : 1149.5922 ; found : 1149.5927 (ESI)

**(3*S*,5*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-12-hydroxy-7-methylene-N-phenyldodec-8-ynamide**




In a 25 mL Schlenk tube under nitrogen equipped with a stirbar were placed Palladium cinnamyl chloride dimer (40.5 mg, 0.078 mmol, 0.1 eq), 4-(2-(di(adamantan-1-yl)phosphino)phenyl)morpholine (Mor-Dalphos) (72.3 mg, 0.156 mmol, 0.2 eq) and Cesium carbonate (254 mg, 0.781 mmol, 1 eq). The flask was evacuated and backfilled 4 times with nitrogen. It was useful to place the Cesium carbonate on top of the other reagents to minimize their blowing around during this step. Separately, vinyl chloride **S3** (400 mg, 0.781 mmol, 1 eq) was mixed with 4-pentyl-1-ol (0.22 mL, 2.34 mmol, 3 eq) in 6 ml of THF under nitrogen. The THF mixture was transferred into the Schlenk tube and the orange mixture was heated to 65 °C and sealed. After 7 hours, TLC (10% EtOAc/hexanes, $KMnO_4$, starting material $R_f$= 0.85, product $R_f$=0.25, pentynol $R_f$=0.10, pentynol ene-yne dimer $R_f$=0.05) showed consumption of pentynol due to head to tail dimerization, but presence of starting material. An additional 0.2 mL of 4-pentyl-1-ol was added and the reaction was stirred for 20 more hours until TLC showed consumption of starting material. The reaction was quenched with 10 mL saturated $NH_4Cl_{(aq)}$ and diluted with 30 mL 90% EtOAc/hexanes. The layers were separated and the aqueous layer was extracted with 2x 20 mL 90% EtOAc/hexanes. The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo.* Purification of the residue by flash chromatography on silica (10% to 20% EtOAc/hexanes) gave 295 mg of ene-yne **S4** (0.527 mmol, 67%) as a clear colorless oil. Characterization data were in agreement with ene-yne S**4** prepared from vinyl iodide with palladium chloride benzonitrile complex (see George Borg's thesis for the data and Chapter 3 for an explanation of the necessity of using separate conditions for Sonogashira coupling on the vinyl chloride).

**(3*S*,5*S*,*Z*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-7-methylene-*N*-phenyl-12-((triethylsilyl)oxy)dodec-8-enamide (80)[51]**




To a solution of alcohol **4** (472 mg, 0.84 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added imidazole (172 mg, 2.52 mmol) and TESCl (211 μL, 1.26 mmol). The reaction was stirred at 0 °C for 20 min, then quenched with saturated $NaHCO_3$, diluted with EtOAc and extracted. The aqueous layer was back-extracted with EtOAc (2x). The organic layers were mixed, washed with saturated $NH_4Cl$ (2x), saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography on silica gel using EtOAc in hexanes (10%) as eluant gave 567 mg ( quant) of amide **80** as a clear colorless oil. Yield: quant. (567 mg);

$R_f$ = 0.36 (90:10 hexanes/EtOAc, UV active, stains blue in CAM);

$[\alpha]^{20}_D$ –14.7 (c = 1.0, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.50-7.52 (m, 2H), 7.30-7.33 (m, 2H), 7.07-7.10 (m, 1H), 5.73 (d, *J* = 11.6 Hz, 1H), 5.50 (dt, *J* = 11.7, 7.3 Hz, 1H), 5.02 (s, 1H), 4.91 (s, 1H), 4.29-4.34 (m, 1H), 3.79-3.87 (m, 1H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.69 (dd, *J* = 14.9 3.7 Hz, 1H), 2.36-2.41 (m, 2H), 2.17-2.23 (m, 3H), 1.80 (ddd, *J* = 12.7, 9.6 Hz, 2.8, 1H), 1.69 (ddd, *J* = 13.9, 9.2,4.0 Hz, 1H), 1.55-1.61 (m, 2H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.94 (s, 9H), 0.91 (s, 9H), 0.61 (q, *J* = 8.0 Hz, 6H), 0.16 (s, 3H), 0.12 (s, 6H), 0.10 (s, 3H);

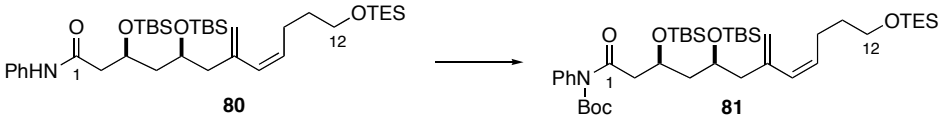
(51) The following characterization data was obtained by Dr. Pascal Bindschädler and the procedure was written by him, and adapted from the one I developed for the series with $C_{12}$ TBS protection.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 169.4, 141.5, 138.5, 132.7, 129.9, 129.1 (2C), 124.0, 119.8 (2C), 116.4, 68.8, 67.7, 62.7, 46.9, 44.3, 43.4, 33.4, 26.13 (3C), 26.11 (3C), 25.6, 18.2 (2C), 7.0, 4.7, –3.8, –4.2, –4.3, –4.6;

IR (film) 3320, 2955, 2930, 2858, 1686, 1671, 1601, 1542, 1499, 1442, 1256, 1096, 1005, 836, 776, 749 $cm^{-1}$;

Exact mass calcd for $C_{37}H_{69}NO_4Si_3$ $[M+H]^+$: 676.4607; found 676.4605 (ESI).

**tert-butyl ((3S,5S,Z)-3,5-bis((tert-butyldimethylsilyl)oxy)-7-methylene-12-((triethylsilyl)oxy)dodec-8-enoyl)(phenyl)carbamate (81)[51]**




To a solution of **80** (567 mg, 0.84 mmol) in $CH_3CN$ (10 mL) at room temperature was added DMAP (205 mg, 1.68 mmol) and $Boc_2O$ (565 mg, 2.52 mmol). The reaction was stirred at room temperature for 30 min, and concentrated under reduced pressure. Purification by chromatography on silica gel using 5% EtOAc in hexanes as eluant gave title compound **81** as a clear colorless oil. Yield: 99% (643 mg);

$R_f$ = 0.45 (90:10 hexanes/EtOAc, UV active, stains blue in CAM);

$[\alpha]^{20}_D$ +6.2 (c = 1.0, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.37-7.40 (m, 2H), 7.31-7.34 (m, 1H), 7.06-7.08 (m, 2H), 5.78 (d, 1H, *J* = 11.7 Hz), 5.51 (dt, *J* = 11.7, 7.3 Hz, 1H), 5.04 (s, 1H), 4.95 (s, 1H), 4.40-4.45 (m, 1H), 3.81-3.86 (m, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.10 (dd, *J* = 16.7, 7.5 Hz, 1H), 2.99 (dd, *J* = 16.7, 4.4 Hz, 1H), 2.22-2.35 (m, 4H), 1.62-1.71 (m, 4H), 1.38 (s, 9H), 0.98

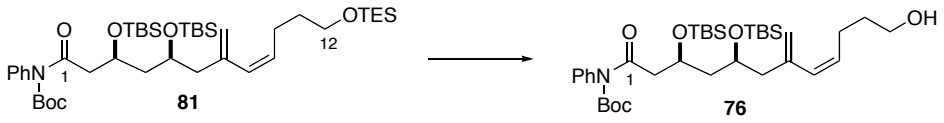
(t, $J$ = 7.9 Hz, 9H), 0.89 (s, 9H), 0.89 (s, 9H), 0.61 (q, $J$ = 8.0 Hz, 6H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.7, 152.9, 142.0, 139.3, 132.3, 130.4, 129.1 (2C), 128.5 (2C), 127.9, 116.2, 83.1, 68.9, 67.0, 62.8, 46.2, 45.8, 45.2, 33.5, 28.1 (3C), 26.23 (3C), 26.19 (3C), 25.6, 18.25, 18.23, 7.0, 4.7, –4.10, –4.13, –4.18, –4.24;

IR (film) 2955, 2856, 1736, 1704, 1459, 1370, 1294, 1255, 1154, 1091, 1005, 836, 775, 746 cm$^{-1}$;

Exact mass calcd for $C_{42}H_{77}NO_6Si_3$ $[M+Na]^+$: 798.4951; found 798.4955 (ESI).

**tert-butyl ((3S,5S,Z)-3,5-bis((tert-butyldimethylsilyl)oxy)-12-hydroxy-7-methylenedodec-8-enoyl)(phenyl)carbamate (76)[51]**




To a solution of **71** (568 mg, 0.73 mmol) in $CH_2Cl_2$ (5 mL) and MeOH (5 mL) at 0 °C was added PPTS (14.5 mg, 0.058 mmol). The reaction was stirred at 0 °C for 2.5 h, then quenched with saturated $NaHCO_3$, diluted with $Et_2O$ and extracted. The aqueous layer was back-extracted with $Et_2O$ (2x). The organic layers were mixed, washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel using hexanes:EtOAc (90:10 to 80:20) as eluant gave title compound **76** as a clear colorless oil. Yield: 94% (455 mg);

$R_f$ = 0.26 (80:20 hexanes/EtOAc, UV active, stains blue in CAM);

$[\alpha]^{20}_D$ +10.8 (c = 1.0, $CHCl_3$);

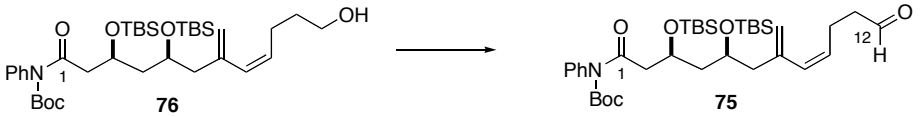
$^1$H NMR (500 MHz, $CDCl_3$) δ 7.37-7.40 (m, 2H), 7.31-7.34 (m, 1H), 7.06-7.07 (m, 2H), 5.81 (d, *J* = 11.6 Hz, 1H), 5.51 (dt, *J* = 11.7 Hz, 7.2 Hz, 1H), 5.06 (s, 1H), 4.94 (s, 1H), 4.42-4.47 (m, 1H), 3.76-3.81 (m, 1H), 3.64 (td, *J* = 6.1, 6.0 Hz, 2H), 3.16 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.96 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.24-2.42 (m, 4H), 1.64-1.78 (m, 5H), 1.37 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.8, 153.1, 141.9, 139.3, 132.1, 130.8, 129.1 (2C), 128.5 (2C), 127.9, 116.5, 83.2, 68.9, 67.1, 62.6, 46.4, 45.5, 45.1, 33.2, 28.1 (3C), 26.3 (3C), 26.2 (3C), 25.4, 18.24, 18.22, –4.06, –4.14, –4.18, –4.22;

IR (film) 2930, 2857, 1736, 1459, 1370, 1294, 1255, 1154, 1090, 836, 775 $cm^{-1}$;

Exact mass calcd for $C_{36}H_{63}NO_6Si_2$ $[M+Na]^+$: 684.4086; found 684.4077 (ESI).

**_tert_-butyl ((3*S*,5*S*,*Z*)-3,5-bis((_tert_-butyldimethylsilyl)oxy)-7-methylene-12-oxododec-8-enoyl)(phenyl)carbamate (75)**




Alcohol **76**, (528 mg, 0.780 mmol, 1 eq) was dissolved in 3 mL $CH_2Cl_2$. Hunig's base (0.429 mL, 2.39 mmol, 3 eq) and DMSO (0.340 mL, 4.78 mmol, 6 eq) were added and the reaction was cooled to 0 °C. $SO_3$-Py (253 mg, 1.59 mmol, 2 eq) was added. After 15 minutes, TLC showed completion (TLC conditions). The volatiles were removed *in*

*vacuo* and the residue was taken up in a minimal amount of $CH_2Cl_2$ and loaded on a pre-equilbrated column which was eluted using 10% EtOAc/hexanes to afford 528 mg (0.780 mmol, 100% ) of aldehyde **75** as a clear colourless oil. This material was judged to be of >95 % purity by $^1$H NMR analysis.

$R_f$ = 0.80 (20 % EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ +6.6 (c = 2.5, $CHCl_3$);

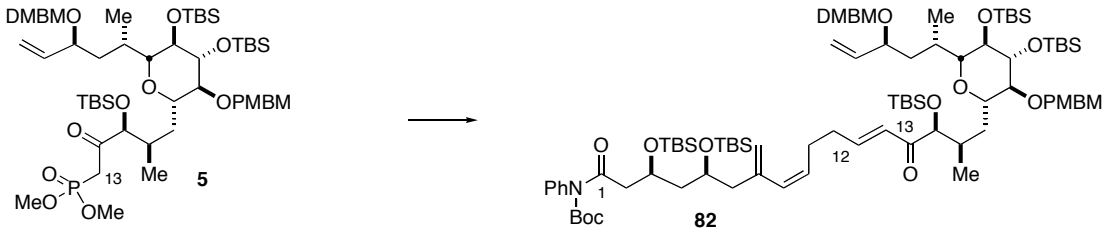
$^1$H NMR (600 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.6 Hz, 1H), 7.37 (ap. t, *J* = 7.3 Hz, 2H), 7.31 (ap. t, *J* = 7.5 Hz, 1H), 7.05 (ap. d, *J* = 7.5 Hz, 2H), 5.84 (dd, *J* = 11.6, 1.3 Hz, 1H), 5.44 (dt, *J* = 11.5, 6.8 Hz, 1H), 5.07 (s, 1H), 4.92 (s, 1H) 4.43- 4.38 (m, 1H), 3.81 (ap. pent, *J* = 6.1 Hz, 1H), 3.09 (dd, *J* = 16.6, 7.3 Hz, 1H) 2.98 (dd, *J* = 16.7, 4.4 Hz, 1H), 2.60- 2.55 (m, 2H), 2.54- 2.50 (m, 2H), 2.27 (ap. d, *J* = 6.3 Hz, 2H), 1.68 (ap. t, *J* = 6.2 Hz, 2H), 1.36- 1.35 (m, 11H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.8, 173.4, 152.6, 141.5, 139.0, 131.6, 129.6, 128.8, 128.2, 127.6, 116.5, 82.8, 68.5, 66.7, 45.7, 45.4, 44.9, 44.0, 27.7, 25.9, 21.5, 18.0, 17.9, -4.4, -4.5, -4.6;

IR (film) 2961.4, 2856.2, 1736.1, 1597.3, 1472.1, 1369.9, 1294.0, 1255.1, 1154.1, 1090.4, 836.4, 775.3 $cm^{-1}$;

Exact mass calcd for $C_{36}H_{61}NO_6Si_2$ $[M+Na]^+$: 682.3930; found 682.3960 (ESI).

**Elaborate HWE Product (82)**




Phosphonate **5** (80 mg, 0.064 mmol, 1 eq) was mixed with aldehyde **75** (85mg, 0.129 mmol, 2 eq) in a minimal amount of $CH_2Cl_2$. The $CH_2Cl_2$ was removed *in vacuo* and the residue was dissolved in 4 mL THF under nitrogen. Cesium carbonate (23 mg, 0.067 mmol, 1.05 eq) was added and the reaction was stirred at room temperature. After 15 hours, the resulting turbid mixture was filtered through Celite® and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (5% to 50% EtOAc/hexanes) to afford 102 mg (0.057 mmol, 89%) of enone **82** as a viscous clear colourless oil. $^1$H N NMR indicated a greater than 20:1 ratio of E: Z double bond isomers. The excess aldehyde was also recovered.

Characterization Data:

$R_f$= 0.60 (25 % EtOAc/hexanes, highly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -15.8 (*c* 3.69, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.39- 7.35 (m, 2H), 7.33- 7.29 (m, 1H), 7.26 (d, *J* = 6.7 Hz, 2H), 7.07- 7.04 (m, 2H), 6.93 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.90- 6.86 (m, 4H), 6.84- 6.81 (m, 1H), 6.48 (dd, *J* = 15.5, 1.3, 1H), 5.80 (d, *J* = 11.5 Hz, 1H), 5.76- 5.69 (m, 1H), 5.47- 5.41 (m, 1H), 5.24 (d, *J* = 17.3 Hz, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 5.03 (s, 1H), 4.88 (s, 1H), 4.83- 4.78 (m, 2H), 4.68 (d, *J* = 5.9 Hz, 1H), 4.66 (d, *J* = 6.0 Hz, 1H), 4.62 (d, *J* = 5.4 Hz, 1H), 4.60 (d, *J* = 4.3 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.45 (d, *J* = 11.3

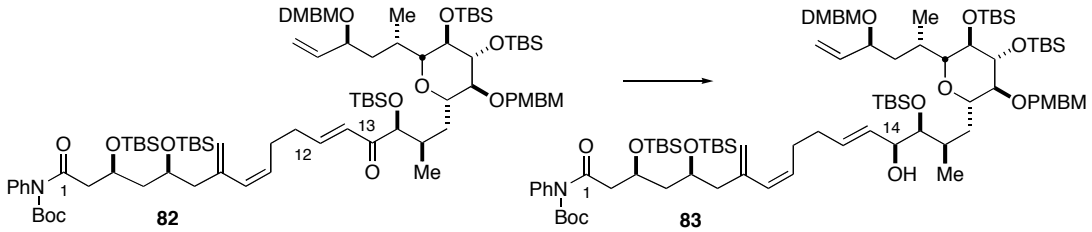
Hz, 1H), 4.42- 4.37 (m, 1H), 4.23- 4.19 (m, 1H), 4.10- 4.07 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84- 3.81 (m, 2H), 3.80 (m, 3H), 3.70- 3.69 (m, 1H), 3.53- 3.49 (m, 1H), 3.42- 3.38 (m, 1H), 3.23- 3.20 (m, 1H), 3.09 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.98 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.40- 2.33 (m, 2H), 2.29- 2.22 (m, 3H), 2.19- 2.12 (m, 2H), 1.90- 1.84 (m, 1H), 1.79- 1.74 (m, 1H), 1.71- 1.66 (m, 2H), 1.62- 1.50 (m, 3H), 1.49- 1.44 (m, 1H), 1.39 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.93- 0.91 (m, 12H), 0.90- 0.89 (m, 18H), 0.88- 0.86 (m, 18H), 0.12- 0.09 (m, 9H), 0.12- 0.09 (m, 9H), 0.07 (m, 3H), 0.05- 0.03 (m, 9H), 0.02 (s, 6H), 0.00 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.3, 173.4, 159.1, 152.6, 148.9, 148.5, 146.5, 141.5, 139.0, 138.9, 131.0, 130.5, 130.3, 129.8, 129.3, 128.8, 128.2, 127.6, 125.7, 120.4, 120.4, 117.0, 116.2, 113.7, 111.1, 110.9, 93.7, 91.6, 84.4, 82.8, 80.0, 79.9, 76.8, 75.7, 75.2, 72.8, 69.4, 69.2, 68.5, 66.7, 55.8, 55.7, 55.1, 45.8, 45.5, 45.0, 41.0, 38.1, 34.2, 32.9, 30.6, 29.6, 27.7, 27.3, 26.1, 26.0, 25.9 (2 signals), 18.2, 18.0 (2 signals), 17.9 (2 signals), 15.1, 13.3, -3.2, -3.8 (2 signals), -4.0, -4.4 (2 signals), -4.5 (2 signals), -4.6, -4.9;

IR(film) 2954.0, 2856.4, 1736.2, 1708.0, 1618.1, 1515.4, 1471.8, 1369.7, 1293.9, 1254.2, 1155.6, 1093.7, 1033.9, 836.9, 775.7 $cm^{-1}$;

Exact mass calcd for $C_{90}H_{153}NO_{17}Si_5$ $[M+Na]^+$: 1682.9877; found 1682.9560(ESI).

**Elaborate Luche Product (83)**



Enone **82** (90 mg, 0.054 mmol, 1 eq) was dissolved in 3 mL THF and 1.5 mL MeOH. Cerium trichloride heptahydrate (40 mg, 0.108 mmol, 2 eq) was added and the reaction was stirred until this dissolved. The reaction was then cooled to -78 °C and $NaBH_4$ (6.1 mg, 0.162 mmol 3 eq) was added as a solid. After 1 hour the reaction was quenched by the addition of 0.3 mL acetone and 3 mL saturated $NH_4Cl_{(aq)}$. The mixture was quickly diluted with 30 mL 90 % EtOAc/hexanes and washed with $H_2O$. The aqueous layers was extracted with 20 mL 90 % EtOAc/hexanes and the combined organic layers were washed with brine and dried over $Na_2SO_4$, then concentrated *in vacuo*. The residue was purified by flash chromatography to yield elaborate Luche product **83** (80 mg, 0.048 mmol, 89 %) as a clear colourless oil.

Characterization Data:

$R_f$= 0.60 (25 % EtOAc/hexanes, highly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -15.3 (*c* 3.05, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.37 (ap. t, *J* = 7.3 Hz, 2 H), 7.31 (ap. t, *J* = 7.3 Hz, 1H), 7.24 (ap d, *J* = 8.8 Hz, 2H), 7.07- 7.04 (m, 2H), 6.89- 6.85 (m, 4H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.76 (ap. d, *J* = 12.7 Hz, 1H), 5.73- 5.68 (m, 2H), 5.49- 5.40 (m, 2H), 5.23 (d, *J* = 12.7 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 5.01 (s, 1H), 4.90 (s, 1H), 4.81- 4.78 (m, 2H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 7.3 Hz, H), 4.59 (d, *J* = 7.8 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 11.2 Hz, 1H), 4.42- 4.37 (m, 1H), 4.03- 3.99 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85- 3.83 (m, 1H), 3.83- 3.80 (m, 1H), 3.80 (s, 3H), 3.70- 3.67 (m, 1H), 3.55- 3.49 (m, 1H), 3.43- 3.40 (m, 1H), 3.20 (dd, *J* = 6.3, 3.4 Hz, 1H), 3.08 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.97 (dd, *J* = 16.6, 4.4, 1H), 2.32- 2.27 (m, 2H), 2.26- 2.22 (m, 2H), 2.14- 2.08 (m, 2H), 1.93- 1.83 (m, 2H), 1.79- 1.72 (m, 1H), 1.69-

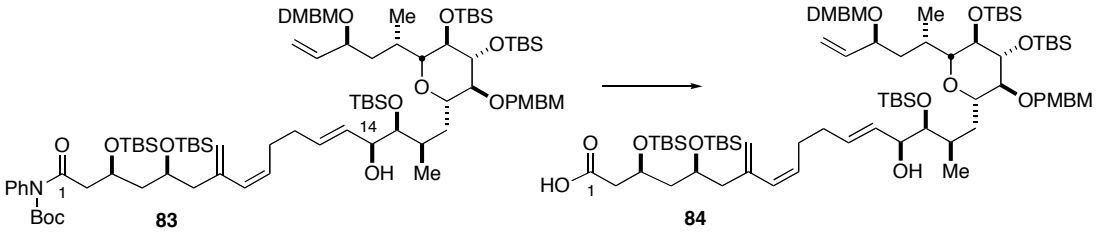
1.66 (t, $J$ = 5.8 Hz, 2H), 1.60- 1.46 (m, 4H), 1.36 (s, 9H), 0.96 (d, $J$ = 6.4 Hz, 3H), 0.93 (d, $J$ = 4.5 Hz, 3H), 0.90 (s, 27H) 0.87 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.11 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.4, 159.1, 152.6, 149.0, 148.6, 141.7, 139.0, 138.9, 131.6, 131.5, 131.2, 130.5, 130.3, 129.8, 129.2, 128.8, 128.2, 127.6, 120.4, 117.1, 116.0, 113.7, 111.2, 110.9, 93.6, 91.6, 84.3, 82.8, 80.1, 78.0, 77.6, 75.5, 75.3, 73.7, 72.8, 69.4, 69.1, 68.6, 66.7, 55.9, 55.7, 55.1, 45.9, 45.5, 44.9, 41.1, 38.2, 36.6, 34.0, 32.7, 30.6, 28.4, 27.8, 26.1, 25.9 (2 signals), 18.4, 18.0, 17.9 (2 signals), 15.8, 13.3, -3.3, -3.9 (3 signals), -4.0, -4.1, -4.4, -4.5 (2 signals);

IR (film) 2930.0, 2856.0, 1737.8, 1515.2, 1463.0, 1369.9, 1253.0, 1155.5, 1093.5, 1033.2, 836.2, 774.9 cm$^{-1}$;

Exact mass calcd for $C_{90}H_{155}NO_{17}Si_5$ $[M+Na]^+$: 1685.0033; found 1685.0001 (ESI).

**Elaborate Seco Acid (84)**




Elaborate Luche product **83** (80 mg, 0.048 mmol, 1 eq) was dissolved in 3 mL THF and cooled to -20 °C. To this solution were added 15 drops of 30 % aqueous hydrogen peroxide. To the homogenous solution were added 7 drops of 1 M $LiOH_{(aq)}$ (an excess) . The reaction was held at -5 °C for 15 hours at which time TLC showed complete

consumption of starting material. To the solution at 0 °C was added saturated $Na_2SO_{3(aq)}$ until a KI/$KIO_3$/Starch peroxide test strip shows the absence of peroxides. The reaction was made acidic to pH paper by the addition of 1 M $NaHSO_4$. The reaction was diluted with 20 mL 90 % EtOAc/hexanes and the aqueous layer was extracted with a further 50 mL of 90 % EtOAc/hexanes. The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica (30 % to 40 % EtOAc/hexanes) yielded 59 mg of elaborate seco acid **84** (0.0396 mmol, 82 %) as a clear colourless very viscous oil.

$R_f$ = 0.20 (50% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -9.6 (*c* 0.32, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.90- 6.86 (m, 4H), 6.83 (d, *J* = 8.0 H, 1H), 5.76- 5.66 (m, 3H), 5.53- 5.46 (m, 1H), 5.44 (dd, *J* = 15.3, 6.6 Hz, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 5.02 (s, 1H), 4.92 (s, 1H), 4.82- 4.79 (m, 2H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.3, 1H), 4.50 (d, *J* = 11.6, 1H), 4.46 (d, *J* = 11.4 Hz, 1H) 4.27 (ap. sext., *J* = 4.5 Hz, 1H), 4.23- 4.18 (m, 1H), 4.03 (ap. t, *J* = 5.7 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (ap. t, *J* = 3.7 Hz, 1H), 3.81 (s, 9H), 3.74 (ap. sext. *J* = 4.0 Hz, 1H), 3.70 (dd, *J* = 6.3, 3.7 Hz, 1H), 3.55- 3.51 (m, 2H), 3.43 (ap. t, *J* = 4.5 Hz, 1H), 3.21 (dd, *J* = 6.3, 3.6 Hz, 1H), 2.56 (dd, *J* = 15.2, 4.7 Hz, 1H), 2.36 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.33- 2.27 (m, 1H), 2.20 (dd, *J* = 13.3, 8.2 Hz, 1H), 2.15- 2.09 (m, 2H), 1.94 – 1.89 (m, 1H), 1.88- 1.83 (m, 1H), 1.79- 1.71 (m, 2H), 1.67- 1.61 (m, 1H), 1.59- 1.53 (m, 1H), 1.53- 1.46 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 27 H), 0.90 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H), 0.11 (s, 6H), 0.10 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H);

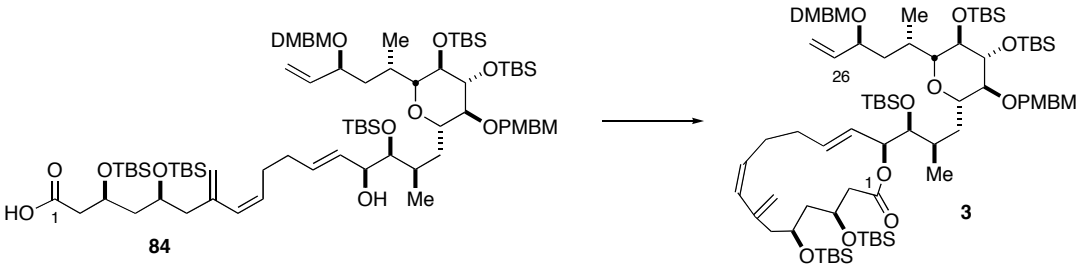
$^{1}$H NMR (600 MHz, $C_6D_6$) δ 7.36 (d, *J* = 8.6 Hz, 2H), 7.03- 7.00 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.87 (d, *J* = 11.6 Hz, 1H), 5.82- 5.70 (m, 2H), 5.64 (dd, *J* = 15.5, 7.6 Hz, 1H), 5.55- 5.49 (m, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 5.08 (s, 1H), 5.03 (s, 1H), 5.01 (d, *J* = 6.8 Hz, 1H), 4.95 (d, *J* = 6.7 Hz, 1H), 4.86- 4.81 (m, 2H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.51- 4.43 (m, 2H), 4.19 (t, *J* = 6.1 Hz, 1H), 4.10 (t, *J* = 4.1 Hz, 1H), 3.94 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.87 (ap. sept., *J* = 3.6 Hz, 1H), 3.85- 3.81 (m, 1H), 3.79 (dd, *J* = 5.7, 2.6 Hz, 1H), 3.69 (dd, *J* = 4.7, 4.4 Hz, 1H), 3.54- 3.50 (m, 1H), 3.52 (s, 3H), 3.42 (s, 3H), 3.31 (s, 3H), 2.58 (dd, *J* = 15.0, 4.6 Hz, 1H), 2.51 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.49- 2.45 (m, 1H), 2.43 (dd, *J* = 13.3, 4.5 Hz, 1H), 2.39- 2.34 (m, 1H), 2.32 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.25- 2.20 (m, 1H), 2.16- 2.10 (m, 1H), 2.08- 2.02 (m, 1H), 1.99- 1.93 (m, 1H), 1.89- 1.80 (m, 2H), 1.78- 1.72 (m, 1H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.08 (s, 9H), 1.05 (s, 18H), 1.01 (s, 9H), 1.00 (s, 9H), 0.28 (s, 3H), 0.27 (s, 3H), 0.26 (s, 3H), 0.25 (s, 3H), 0.25 (s, 3H), 0.24 (s, 3H), 0.19 (s, 6H), 0.14 (s, 3H), 0.11 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.2 (broad signal), 159.2, 149.0, 148.6, 141.3, 139.0, 132.0, 131.8, 131.7, 131.1, 130.5, 129.9, 129.8, 129.3 (2 signals), 120.5, 117.2, 116.3, 113.8, 111.2, 110.9, 93.6, 91.6, 84.4, 80.1, 78.0, 77.7, 75.5, 75.4, 73.8, 72.8, 69.5, 69.3, 69.1, 68.5, 66.9, 55.9, 55.8, 55.2, 46.2, 43.8, 41.3, 41.1, 38.2, 34.0, 32.7, 30.6, 29.7, 28.5, 26.1, 26.0, 25.8, 25.7, 18.4, 18.3, 18.0, 17.9 (2 signals), 17.7, 15.8, 13.3, -3.3, -3.8, -3.9, -4.0, -4.1, -4.2, -4.5, -4.6, -4.9;

IR(film) 3200 (broad), 2928.3 2855.8, 1711.8, 1612.3, 1515.4, 1463.5, 1251.6, 1097.8, 1033.4, 836.5, 775.2 $cm^{-1}$;

Exact Mass Calc. for $C_{79}H_{142}O_{16}Si_5$ $[M + Na]^+$ : 1509.9036; found : 1509.8856 (ESI)

**Elaborate *Z*- Diene (3)**




In a flame dried 5 mL flask were placed DMAP (24 mg, 0.198 mmol, 5 eq) and 1-methyl-6-nitro-benzoic anhydride (34 mg, 0.099 mmol, 2.5 eq) under nitrogen. These were dissolved in 1 mL $CH_2Cl_2$. In a separate flask, elaborate seco acid **84** (59 mg, 0.040 mmol, 1.0 eq) was dissolved in 5 mL $CH_2Cl_2$ and added at the rate of 0.5 mL/hr by syringe pump. The syringe and needle were washed with an additional 1 mL of $CH_2Cl_2$. The reaction was stirred an additional 8 hours after the addition was complete. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (10% EtOAc/hex) to yield 59 mg of elaborate Z macrocycle (0.04 mmol, quant) as a clear colourless oil.

$R_f$ = 0.50 (20% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -25.2 (*c* 1.98, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.89- 6.86 (m, 4H), 6.83 (d, *J* = 7.9 Hz, 1H), 5.76 (d, *J* = 11.3 Hz, 1H), 5.71 (ddd, *J* = 17.9, 10.1, 7.9 Hz, 1H), 5.63- 5.57 (m, 1H), 5.38- 5.28 (m, 2H), 5.23 (d, *J* = 17.0 Hz, 1H), 5.19 (d, *J* =10.3 Hz, 1H), 5.02 (s, 1H), 5.00 (t, *J* = 7.7 Hz, 1H), 4.82- 4.79 (m, 3H), 4.66- 4.64 (m, 2H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H),

4.20- 4.17 (m, 2H), 4.16- 4.12 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.87- 3.86 (m, 1H), 3.81 (s, 3H), 3.73- 3.70 (m, 1H), 3.68 (ap. d, *J* = 8.4 Hz, 1H), 3.52- 3.48 (m, 1H), 3.43- 3.41 (m, 1H), 3.17 (t, *J* = 4.8 Hz, 1H), 2.60 (dd, *J* =14.5, 8.3 Hz, 1H), 2.49 (dd, *J* = 14.6, 3.2 Hz, 1H), 2.35 (dd, *J* = 13.6, 3.5 Hz, 1H), 2.31- 2.26 (m, 1H), 2.18 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.15- 2.11 (m, 1H), 2.10- 2.04 (m, 1H), 1.96- 1.90 (m, 1H), 1.83- 1.77 (m, 1H), 1.77- 1.71 (m, 1H), 1.54- 1.49 (m, 1H), 1.48- 1.39 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 18H), 0.89 (s, 18H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), 0.11 (s, 3H), 0.11- 0.10 (m, 12H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.5, 159.1, 149.0, 148.6, 141.2, 139.0, 133.3, 132.0, 130.9, 130.5, 129.9, 129.2, 126.7, 120.4, 117.1, 113.7, 111.2, 110.9, 93.4, 91.6, 84.8, 80.2, 77.9, 75.9, 75.1, 75.1, 75.0, 72.8, 69.5, 69.1, 67.4, 66.9, 55.9, 55.7, 55.2, 46.0, 43.5, 43.3, 40.8, 39.4, 32.2, 31.5, 31.0, 29.7, 28.6, 26.0 (3 signals), 25.9, 18.4, 18.0 (3 signals), 13.8, 13.5, -3.4, -3.8, -3.9, -4.0 (2 signals), -4.1, -4.2, -4.5, -4.7, -4.8;

IR(film) 2953.5, 2959.7, 1731.7, 1515.0, 1470.7, 1251.0, 1098.3, 1034.3, 836.4, 774.5 $cm^{-1}$;

Exact Mass Calc. for $C_{79}H_{140}O_{15}Si_5$ $[M + Na]^+$ : 1491.8930; found : 1491.8777 (ESI)

# *Chapter 5*

## Diels–Alder Studies: Iminium Synthesis and Activation[1,2]

### I. Efficent Preparation of Dienophiles

According to the synthesis plan described in the end of chapter 3, spiro-prorocentrimine **1** would arise from a late-stage Diels–Alder reaction of imine **2** and macrocyclic *Z*- diene **3** followed by subsequent transformations (Figure 1). This chapter describes the synthesis of derivatives of **2** and studies of their use in Diels–Alder reactions.

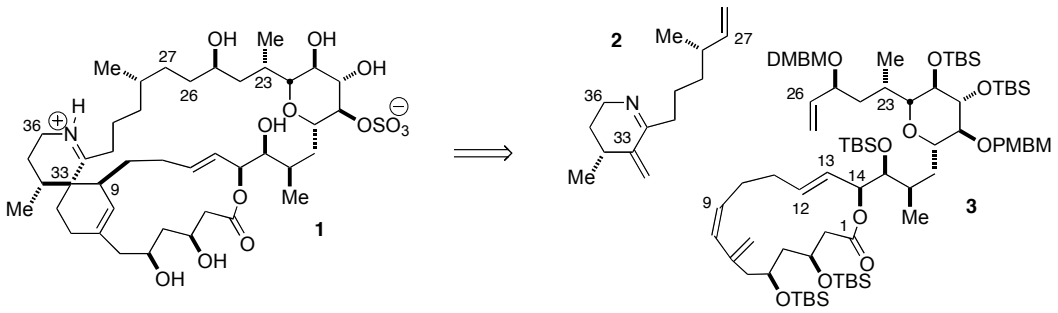



**Figure 5.1** Targeted disconnection of spiro-prorocentrimine.

Initial efforts focused upon the feasibility of elaborating intermediate **4**, prepared by Dr. Anna Chiu as I had inherited 5 g of this material. A sequence of reactions to prepare **2** was run once on a trial scale (Scheme 5.1).

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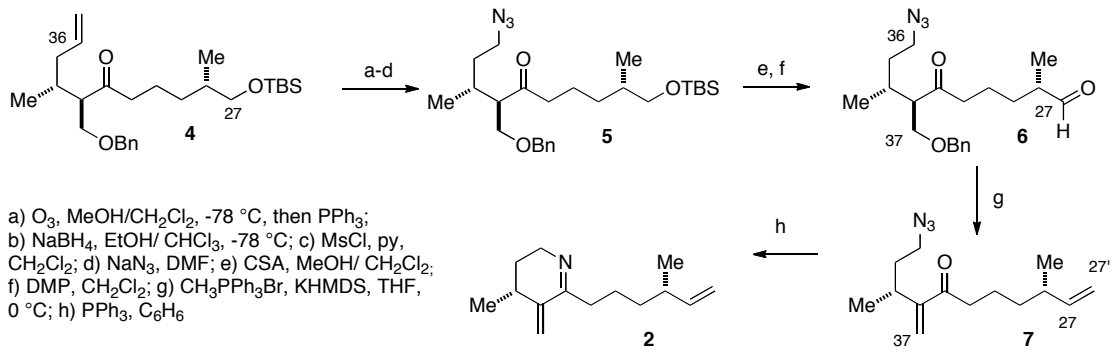
(1) Portions of the work discussed in this chapter were conducted in conjunction with Dr. Pascal Bindschadler and Dr David Marcoux. This is indicated in the appropriate sections.

(2) Adapted in part with permission from Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A.; "Effect of Counterion Structure on Rates and Diastereoselectivities in α,β-Unsaturated Iminium-Ion Diels–Alder reactions" *Org Lett.* **2011**, *13*, 3758- 3761. © 2011 by The American Chemical Society.

**Scheme 5.1**

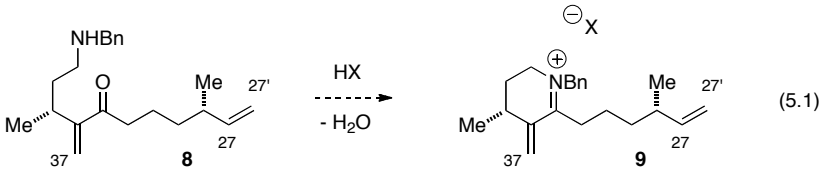



Intermediate **4** could be elaborated to azide **5** in the four step sequence developed by Dr. Anna Chiu. Selective deprotection of the TBS protecting group at the $C_{26}$, alcohol was followed by oxidation to afford aldehyde **6**. This could be exposed to methylidenetriphenylphosphorane to afford olefin **7**, with concomitant and desired elimination of the benzyloxy at $C_{37}$. Exposure to triphenylphosphine in benzene did result in Staudinger reduction and an aza-Wittig reaction, to afford what was tentatively assigned as desired fragment **2**. Compound **2** proved to be unstable, surprisingly volatile, and possessed an appalling odour. I did not regard compound **2** as a viable synthon for several reasons. Preparation of **2** on a large scale was envisoned to be difficult, due to scalability issues I encountered with the transformation from **4** to **5**.[3] It was also feared that any epimerization that occurred on aldehyde **6** may not be detectable since the two stereocentres are quite far apart.[4] As cyclic iminiums are postulated to be the centre of biological activity in these toxins, and as **2** is a Michael acceptor, I also wished to minimize handling of such a compound.

(3) These transformations involve the selective reduction of an aldehyde at $C_{36}$ in the presence of a ketone at $C_{32}$, which I found did not scale well in my hands.

(4) See section VI of this chapter for validation of this fear.

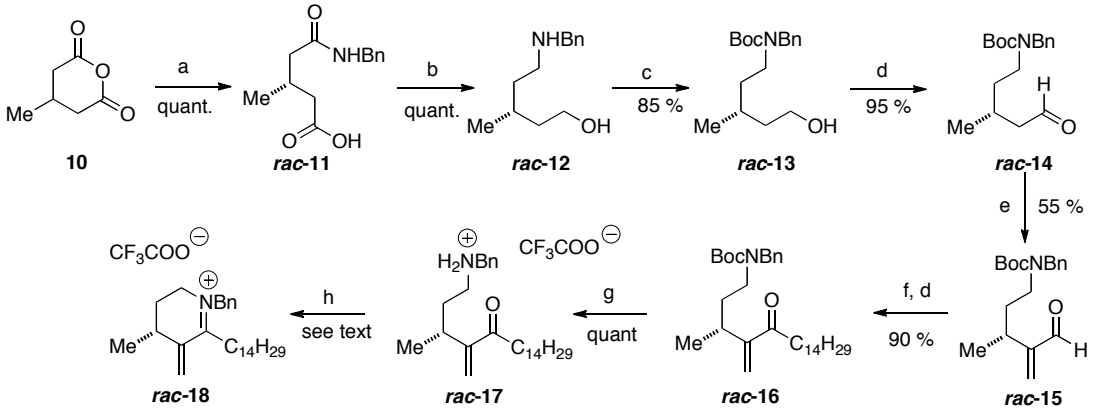
Since the target dienophile contained a benzyl group on the iminium, it was decided to investigate a new synthesis of the dienophile incorporating the benzyl group at an early stage, synthesizing a compound such as **8** bearing both a secondary amine and a ketone, and cyclizing the secondary aminine on the ketone of the enone to form benzyl iminium **9** directly (equation 5.1).




(5.1)

In order to test this principle rapidly, I synthesized a racemic model system. Glutaric anhydride **10** was opened by benzylamine, and the resulting amide acid **rac-11** was reduced to amino alcohol **rac-12** by the action of $LiAlH_4$ (Scheme 5.2). The nitrogen could be selectively Boc protected to give **rac-13**.

**Scheme 5.2**




a) $BnNH_2$, $CH_2Cl_2$; b) $LiAlH_4$, THF, 66 °C; c) $Boc_2O$, $CH_3CN$, 40 °C; d) $SO_3$•py, *i*-$Pr_2NEt$, DMSO, $CH_2Cl_2$; e) $Me_2NH_2Cl$, $CH_2O_{(aq)}$, 70 °C f) $C_{14}H_{29}MgCl$, THF, 0 °C; g) TFA, $CH_2Cl_2$; h) $CDCl_3$, 4 days

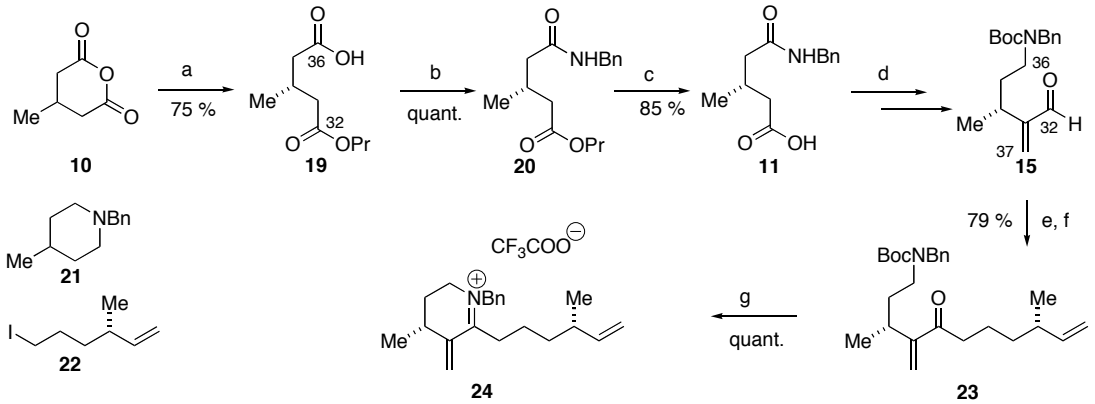
At this point, NMR analysis was complicated by the signifigant broadening and multiplying of signals in the spectra, which persisted in all compounds until the removal

of the Boc group. The alcohol was oxidized to aldehyde **rac-14**, and the exo methylene group was installed by a Mannich reaction to give enal **rac-15**.[5]

Addition of a Grignard reagent in the 1,2 sense to the enal, followed by oxidation allowed the preparation of enone **rac-16**.[6] Exposure of this compound to TFA, resulted in the removal of the Boc group, and the formation of ammonium salt **rac-17**. The cyclization of this compound to iminium **rac-18** occurred spontaneously over several days in chloroform-d. Alternatively, the reaction could be accelerated by the addition of molecular sieves. In working with a related series of compounds, Dr. David Marcoux developed the most efficient cyclization protocol, which involved adding a drop of TFA to a solution of the salt in chloroform, and refluxing until cyclization was complete (typically around 2 hours for the benzylamines).

With this proof of principle in hand, we needed to develop a non-racemic synthesis, and use the actual side chain. This was carried out primarily by Dr. Pascal Bindschädler (Scheme 5.3)

**Scheme 5.3**




a) Armano Lipase, *n*-PrOH, *n*-$Pr_2O$ ; b) $COCl_2$, DMF, $CH_2Cl_2$, then $BnNH_2$; c) LiOH, $H_2O$/THF/DMF; d) Scheme 5.2 b- e
e) *t*-BuLi, **22**, -90 °C, then **15**; f) $SO_3$•py, *i*-$Pr_2NEt$, DMSO, $CH_2Cl_2$; g) TFA/ $CH_2Cl_2$

(5) Ragoussis, V.; Giannikopoulos, A.; Skoka, E.; Grivas, P. *J. Agric. Food. Chem.* **2007**, *55*, 5050-5052.

(6) This Grignard reagent was chosen to mitigate potential volatility of any intermediates.

The stereocentre at $C_{34}$ was set by desymmetrization of glutaric anhydride **10** using an enzymatic method desymmetrization.[7] The resulting acid ester **19** was obtained in 94% ee as determined by chromatography of the benzyl amide derivative on a Chriacel OD column. Benzyl amide **20** was formed by forming an acid chloride, and subsequent reaction with 2 equivalents of benzylamine. An initial attempt to reduce the amide ester resulted in the formation of achrial benzyl piperidine **21**.[8] Accordingly the ester was hydrolyzed using lithium hydroxide to form the amide acid **11**. It should be noted that this step resulted in a signifigant degredation of the enantiomeric ratio of these compounds, which was undetected to by us at the time.[9] Section IV of this chapter contains both the rationalization for and solution to this problem. Several important findings were made with this material despite the low enantiomeric ratio, so this is why these results are included. All steps up to the formation of the enal were conducted identically with the racemic series, ultimately yielding enal **15**. Dr. Bindschadler prepared sidechain iodide **22** from (*S*)- Citronellol using a known procedure.[10] We initially encountered difficulty with the lithium halogen exchange due to the propensity of this substrate to undergo a 5-exo trig cyclization, as also reported by Bailey.[11] A solution to this problem was found by Dr. Bindschädler by running the reaction in small batches, which presumably allowed for a much more rapid dispersal of the heat generated in the lithium halogen exchange to the surrounding cryostat. Oxidation to **23** was followed by

(7) Ito, H.; Inoue, T.; Iguchi, K. *Org. Lett.* **2008**, *10*, 3873-3876.

(8) For an analogous transformation mediated by $BH_3$•$SMe_2$ see: Venuti, M. C.; Ort, O. *Synthesis*. **1988**, 985-988.

(9) As described in section VI I estimate the e.r. of this material dropped to approximately 65:35.

(10) Mori, K.; Masuda, S.; Suguro, T. *Tetrahedron*, **1981**, *37*, 1329-1340. The ee of the citronellol, obtained from Sigma Aldrich, was determined to be greater than 99% by comparison with racemic citronellol. Conditions were injection of 1 µl of a 10mg/mL ether solution of citronellol, with a 100: 1 split on a Beta Dex 225 column, 30 minutes at 90 °C, followed by a 4 °C/ minute ramp to 170 °C. I thank Ms. Naomi Rajapaksa for her assistance with this determination. The (*S*) configuration was confirmed by optical rotation measurements.

(11) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720-5727.

Boc removal and cyclization to iminium **24** occurred in a similar fashion to the racemic model system. It should be noted in retrospect that despite the fact that integrity of the stereocentre at $C_{34}$ had been compromised, compounds **23** and **24** appeared homogenous by $^{1}H$ and $^{13}C$ NMR. This means the stereocentres were too distant to show the epimerization that will be explained in section VI.

## II. Reevaluation of Mode of Activation of Dienophiles

Dr. Pero had observed that some decomposition of the diene in the course of his experiments with methyl triflate (Chapter 3, Scheme 3.8). He blamed this decomposition on adventitious triflic acid.[12] Since superstoichiometric TFA had been used in the iminium formation, it seemed prudent to develop a method of purifying the iminium of any unwanted Bronstead acids. The 3,5-BArF counterion was initially developed as a phase transfer reagent,[13] before achieving its current prominence as a less coordinating counterion in organometallic chemistry and I knew from my preparation of some hydrogenation catalysts in chapter 4 that some 3,5-BArF metal salts could be purified by chromatography with dichloromethane. It was envisioned that iminium BArFates could be used to chromatographically separate the iminium ions from more polar bronstead acids, without using protic (and nucleophillic) eluants such as methanol in chromatography.[14] Accordingly, iminium BArFate **25** was prepared from iminium **18** by counterion exchange with sodium BArFate **26** in ether, and purified by chromatography

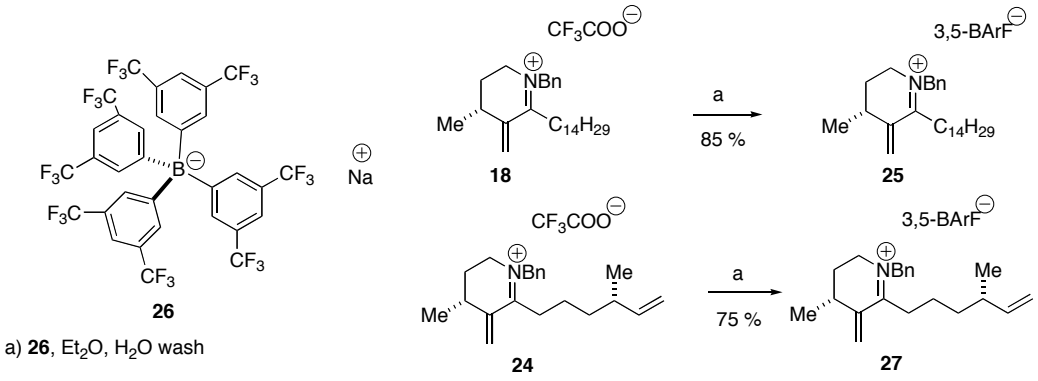
(12) Generation of triflic acids from metal triflates has frequently caused confusion in the studies of reactions mediated by metal triflates. The analogy may be extended to alkyl triflates. See: Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem*. **2011**, *76*, 9353-9361. The term Hidden BrØnsted Acid catalysis was used in this paper.

(13) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn*. **1984, *57*,** 2600- 2604. The preparation of the BArFate in the above paper may lead to explosion. For a safe preparation of sodium 3,5-BArFate, see: Yakelis, N. A.; Bergman, R. G. *Organometallics*, **2005**, *24*, 3579-3581.

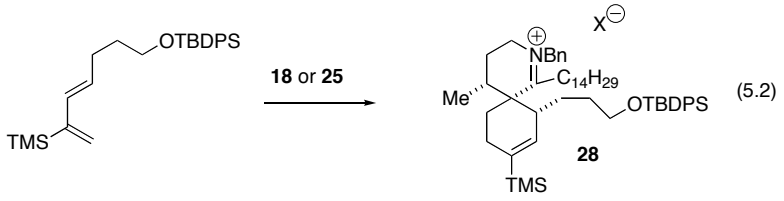
(14) This fear ultimately turned out to be unfounded, as the iminium ions are stable even as methanol solutions.

on silica gel using dichloromethane as eluent (Scheme 5.4). $^{19}F$ NMR studies verified the absence of any residual TFA. This procedure was repeated with iminium **24** to afford BArfate **27**.

**Scheme 5.4**

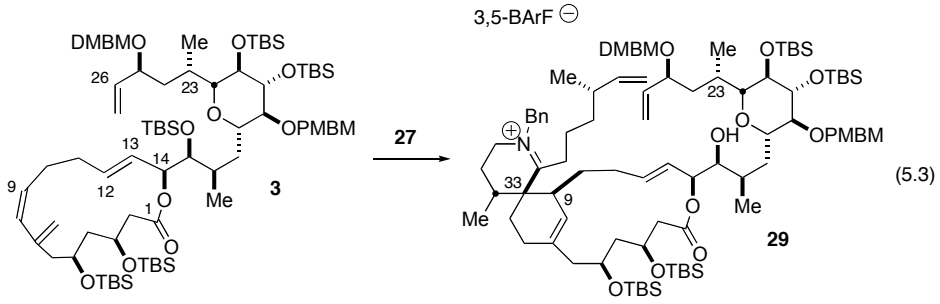



With the model system in hand, I attempted some Diels–Alder studies using diene **28**, available from the work of Dr. George Borg (Equation 5.2). I made the observation was that in the Diels–Alder reactions with **18** and **25**, the iminium BARFates were consumed faster than the trifluoroacetate in reactions with otherwise similar concentrations of reagents. Product **rac-28** was generated in a 7:1 dr with the *endo* isomer being dominant. It appeared that the reaction with BArF reached the halfway point in about a third of the time as the trifluoroacetate. No quantitative studies were performed, however this rate acceleration reinforced the value of using the BARFate as the counterion.




A more pressing observation in these reactions was that the benzyl group remained on the iminium in both the TFA and BArFate cases on adduct **28**. I believed that this may have been a consequence of different steric demand between the model system and the real system. Accordingly, the actual *Z* Macrocyclic diene **3** was allowed to react with benzyl iminium **27**. Because of the small quantity of macrocyclic diene **3** available at the time, a

concentration above 0.05 M could not be achieved, and the reaction had to be heated to 60 °C for several days in chloroform-d. Regardless of this pitfall, some product **29** was isolated with very similar chemical shifts to those of Pero's Diels–Alder adducts (Equation 3). It should be noted that since **27** was not diastereomerically pure, **29** was presumably not formed as a diastereomerically pure compound. This fact was not appreciated at the time, but will be elaborated on in section VI.[15]



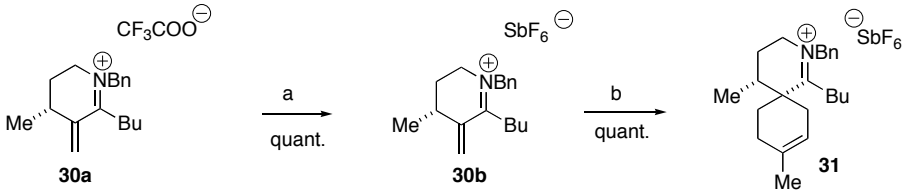

(5.3)

At the time I believed the stereochemistry had the desired configuration at $C_{33}$, but the results in Chapter 6, Section I suggest the configuration was as drawn, with the opposite configuration at $C_{33}$. Regardless of stereochemical matters, it was clearly evident that the benzyl group was still present in these systems. It was speculated that the hexafluoroantimonate used by Dr. Pero had some special property in accelerating the solvolysis of the reaction. Another iminium, **30a**, had been prepared from **15** with a butyl side chain to simplify NMR interpretation. Hexafluoroantimonate **30b** was prepared from counterion exchange with TFA salt **30a**, exploiting the pKa difference between hydronium hexafluoroantimonate and TFA and driving the reaction to completion via azetropic reomoval of the TFA. The addition of methanol during the counterion exchange was necessary to dissolve the hexafluoroantimonic acid during the counterion exchange. This did not result in decomposition of the iminium, emphasizing its stability. The

(15) The results in section I of chapter 6 suggest that the undesired enantiomer of **27** may react faster with *E*-macrocyclic dienes, which are formed under the conditions noted. Consequently the stereocentre at $C_{33}$ may be flipped from what is shown. Insufficent material was prepared to allow full characterization. A full explaination and solution to this problem, which was not appreciated when this Diels–Alder reaction was first carried out is found in Chapter 6.

iminium hexafluoroantimonate could not be purified by chromatography using dichloromethane alone, however, chromatography with 10% methanol in dichloromethane worked well and no decomposition resulted. No macrocycle **3** was available at this point, so **30b** was allowed to react with isoprene to afford **31**. Compound **31** also retained the benzyl group, even after chromatography in the presence of methanol (Scheme 5.5).

**Scheme 5.5**



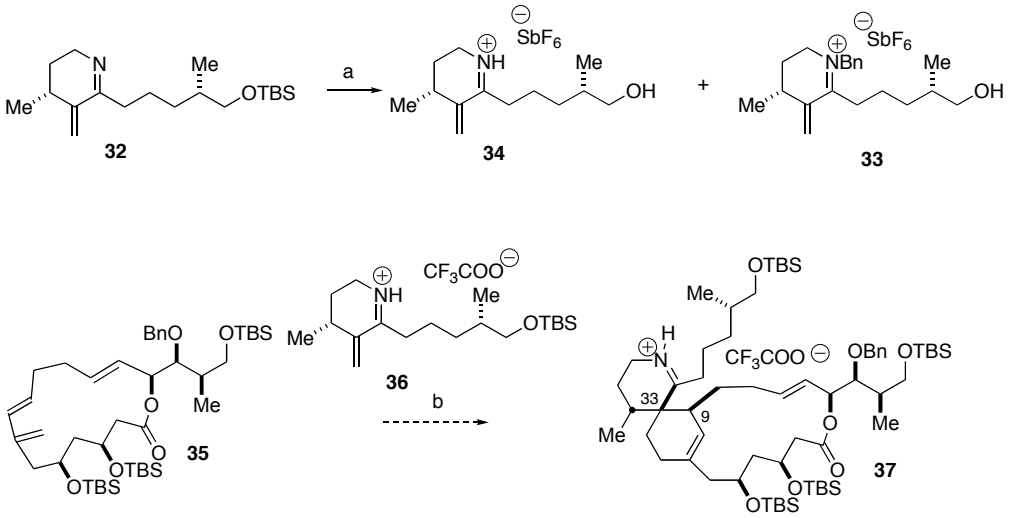

a) $HSbF_6 \cdot 6H_2O$, MeOH, $CH_2Cl_2$ b) isoprene, $CH_2Cl_2$

At this point, I felt I had overestimated the ease of solvolysis of the benzyl group from the iminium, since compounds **30** and **31** were both stable towards chromatography. I began to question if the benzyl group had actually been installed in the alkylation done by Dr. Pero. Inspection of Dr. Pero's NMR data and mass spectral data for the alkylation of **32** to form **33** indeed showed that only very small quantities of the benzyl iminium **33** had been formed, and the dominant product was the protonated iminium **34** with hexafluoroantimonate as the counterion (Scheme 5.6).[16] This result was surprising at first, as Dr. Borg had demonstrated even the more reactive *E* macrocyclic diene **35** did not react with a protonated iminium **36** that had TFA as the counterion.[17] No cycloadduct **37** was detected. A logical explaination was that the counterion effect was responsible for the reactions in the Pero examples, and that the enhanced electonegativity of alkylation was not in fact necessary for the Diels–Alder reaction to proceed.

(16) Dr. Pero had attributed the base peak corresponding to the mass of **34** in his mass spectral data as indicating ease of solvolysis. A small peak corresponding to the mass of **33** was observed. Since Dr. Pero used crude material in the Diels–Alder reaction after the alkylation, the presence of the benzyl group was inferred by $^1$H NMR from peaks that actually arose from benzyl bromide and benzyl alcohol. I had the advantage of comparison with an authentic benzylated iminium.

(17) Borg, G. *PhD. Thesis.*, Harvard University, **2007**. Page 70. Scheme 3.10.

**Scheme 5.6**




a) $AgSbF_6$, BnBr, $CH_2Cl_2$ b) **35** + **36**, $CH_2Cl_2$, 40 °C

It is postulated that the conditions Pero used may form an insoluble silver/benzyl bromide complex, which is not a competent alkylating agent. Upon filtration of the reaction, adventitious water reacts with this complex, releasing hexafluoroantimonic acid which protonates the iminium.[18] Dr. Pero's observation of reaction with this iminium was not due to the presence of an electronegative group, but was because of the counterion effect, that had first inadvertently been recognized with the BArF salt. As described in the next two sections, a rational synthesis of protonated iminium hexafluoroantimonates was developed, and they were found to be excellent dienophiles. Later work by Dr. Marxcoux and Dr. Bindschädler resulted in a quantitative analysis of the counterion effects in protonated iminiums using a variety of counterions. Importantly it was demonstrated that hexafluoroantimonate was as effective as promoting the Diels- Alder reaction as BArFate. Triflate was similar in reactivity to these "ate" ions. Dr. Marcoux also conducted an important competition study, where he found that the alkylated iminiums actually react at a slower rate than the protonated iminiums. The results of

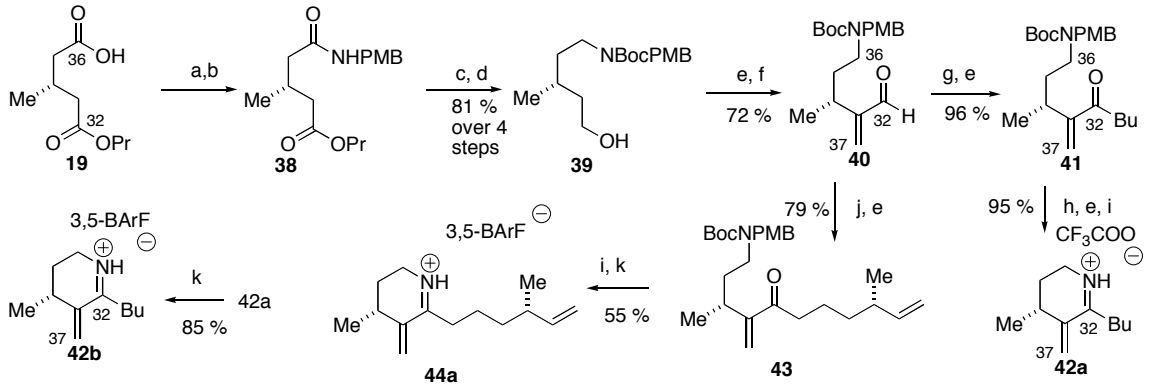
(18) The mixture of silver hexafluoroantimonate and benzyl bromide in the presence of an imine results in the immediate formation of a thick precipitate. The intermedicy of tropylium salts may be possible. Tropylium salts are not soluble in non-polar organic solvents, but are also not known to react with water. It is not clear what effect an imine base would have. See: Garfunkel, E.; Reingold, D. *J. Org. Chem*. **1979**, *44*, 3725-3725.

these studies have been published.[2] It can therefore be reasoned that the methylated iminium triflate also showed a rate acceleration relative to Borg's examples because of this counterion effect and not because of the electronegativity of the methyl substituent.

### III. Further Exploration of the Counterion Effect

With the reinterpretation of Pero's results in hand, the preparation of the dienophile was altered to contain a more readily removable PMB group instead of the benzyl group with the aim of synthesizing protonated iminiums. I first carried out the synthesis of a racemic model to scope out the viability of the route, in complete analogy to scheme 5.2. Dr. Bindschädler prepared the chiral material with the elaborate side chain. Synthesis of the chiral compound is shown in Scheme 5.7.

**Scheme 5.7**



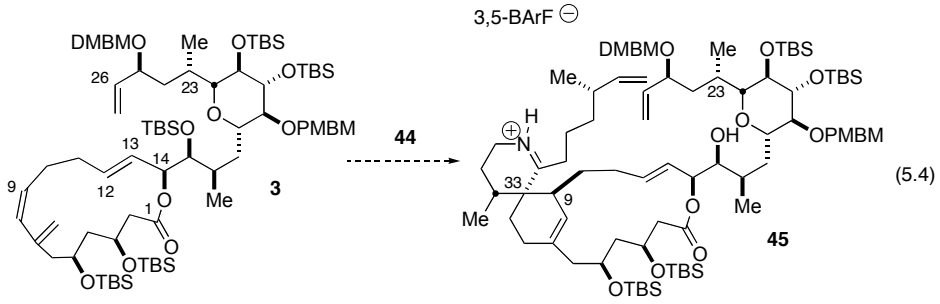

a) $COCl_2$, DMF, $CH_2Cl_2$, then $PMBNH_2$; b) LiOH, $H_2O$/THF/DMF; c) $LiAlH_4$, THF, 66 °C, d) $Boc_2O$, $CH_3CN$, 40 °C e)$SO_3$•py, *i*-$Pr_2NEt$, DMSO, $CH_2Cl_2$; f)$Me_2NH_2Cl$, $CH_2O_{(aq)}$, g) *n*-BuLi, THF, -78 °C; h) CAN, $CH_3CN$, $H_2O$, i) TFA, $CH_2Cl_2$
j) *t*-BuLi, **22**, -90 °C, then **40**; k) **26**, $Et_2O$, $H_2O$ wash

Removal of the PMB with DDQ proved to be infeasible, presumably due to the electron withdrawing nature of the BOC group. Fortunately the stronger oxidant CAN was able to cleanly remove the PMB group. Cyclization occurred more rapidly than with the benzyl iminiums, and it should be noted cyclization occurred even in the course of the removal of the BOC group. PMB acid **38** had a degraded enantiomeric excess that was not known at the time, as with the prior benzylated species. Enal **40** could be elaborated to model

enone **41** and finally iminium **42**, or elaborate enone **43** (which at the time we did not appreciate existed as a mixture of diastereomers) which was transformed to iminium **44**.

Both **42** and **44** were more polar than the corresponding *N*-benzyl iminiums, but could still be purified by flash chromatography on silica gel with 10% MeOH in $CH_2Cl_2$, with either trifluoroacetate or 3,5-BArF counterions.

Unfortunately, reaction of BArF iminium **44** with Z macrocycle **3** resulted in decomposition of **3** (equation 5.4). Nothing attributable to desired adduct **45** could be isolated. It was decided to construct a simpler model macrocycle to attempt to deconvolute the Diels–Alder reaction on less precious material.

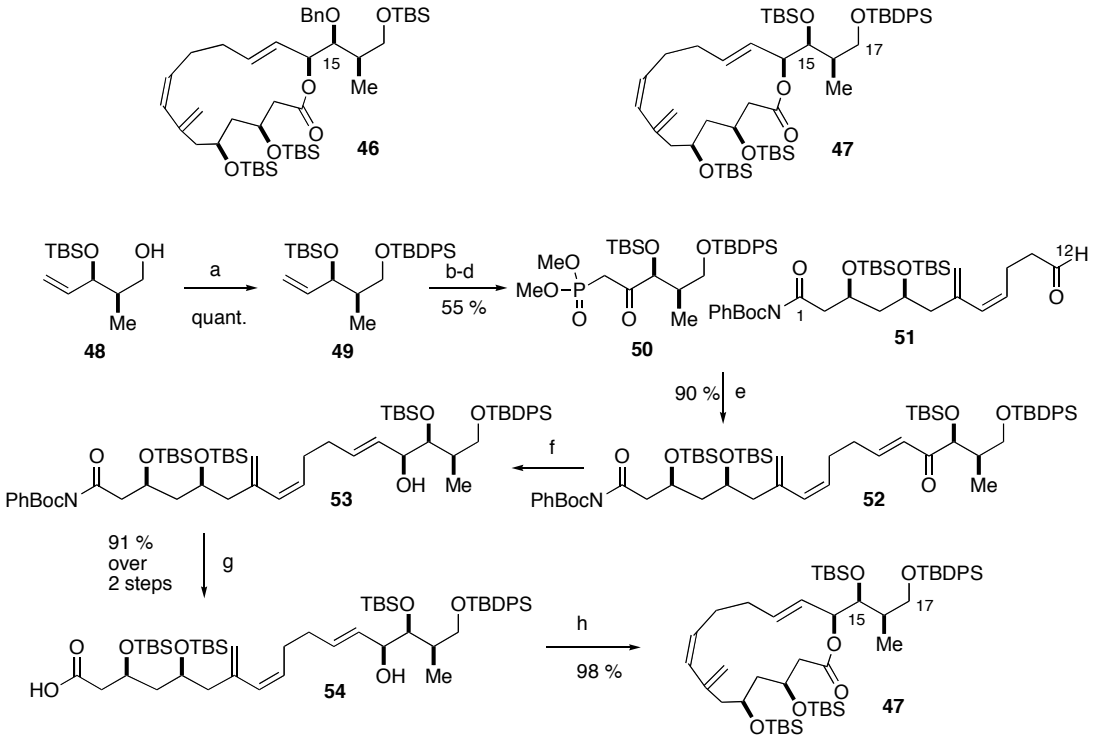



(5.4)

## IV. Preparation of a Simplified Macrocyclic Diene Model

A simpler model macrocycle **46** was available from the work of Borg, that had been employed by Pero in the course of his Diels–Alder studies. However this model bore an earlier and defunct protecting group strategy (with a benzyl group at the $C_{15}$ alcohol), so it was decided to update the synthesis of the model to reflect the most current protecting group strategy. Macrocycle **47** was targeted and its synthesis is described in Scheme 5.8. Alcohol **48** was protected with a TBDPS group, and the olefin in compound **49** was transformed to to β-keto phosphonate **50** in a three step sequence. HWE reaction with aldehyde **51** was uneventful, and Luche reduction of **52** produced compound **53**. In this case, **52** and **53** could be resolved by TLC, simplifying analysis of the the reaction. Imide cleavage gave seco acid **54** and Shiina macrolactonization gave model macrocycle **47**.

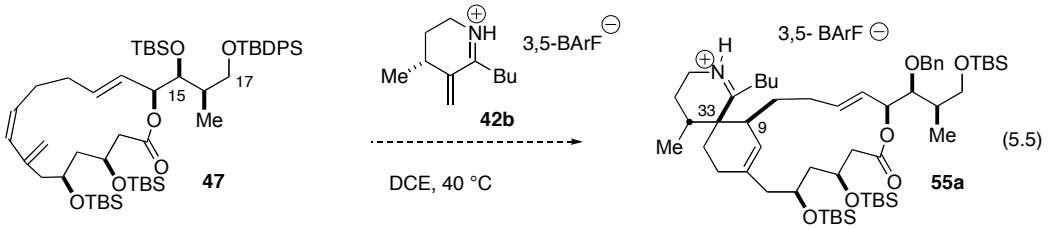
**Scheme 5.8**




a) TBDPSCl, im, $CH_2Cl_2$; b) $O_3$, $CH_2Cl_2$, -78 °C, then $PPh_3$ c) *n*-BuLi, $(CH_3O)_2CH_3P{=}O$, THF, -78 °C; d) DMP, $CH_2Cl_2$; e) *n*-BuLi, **50**, THF, then **51**, 0 °C, f) $CeCl_3{\bullet}7H_2O$, $NaBH_4$, MeOH, THF, -60 °C; g) $LiOH_{(aq)}$, $H_2O_{2(aq)}$, THF, -5 °C; h) MNBA, DMAP, $CH_2Cl_2$

## V. Optimization of the Dienophile Activation

Reaction of this model macrocycle with proton iminium BArFate **42b** also resulted in decomposition (Equation 5.5). Produt **55a** was not apparent.

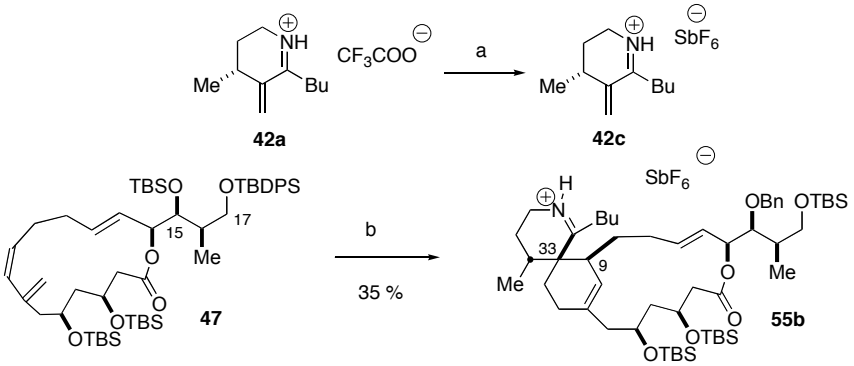



Since similar conditions to Pero were being used, and a clean reaction was not obtained, I made a final attempt to switch the counterion back to hexafluoroantimonate, which was used in Dr. Pero's system.[19] Gratifyingly cycloadduct **55b** was obtained in modest yield after chromatography (Scheme 5.9). As before, it should be noted that at the time I

(19) Again, since **42** was employed as a scalemic mixture, **55** may have been obtained as a diastereomeric mixture that was not readily apparent by $^1H$ NMR. See footnote 17.

conducted the reaction, I believed I had accessed the desired stereochemistry at $C_{33}$. The product is shown with what is currently believed to be the obtained stereochemistry at $C_{33}$. Chapter 6 will contain further details on the stereochemistry of the Diels–Alder adducts. There are a several possible rationales for the divergent outcome between hexafluoroantimonate **42c** and BArFate **42b**. One possibility is that the 3,5- BArFate is more dissociated from the iminium, and the proton is more free to be transferred to diene **47**, ultimately resulting in destructive reactions. It should be noted that **42c** and **42b** have similar NMR spectra, but it is unclear to what extent counterion association would peturb NMR spectra. Another possibility is that the BArFate engages in some sort of π stacking interaction with **47**, changing the electronic environment around the diene and opening a possibility for a distructive interaction. The third possibility is that **43b** contains some sort of impurity that was not detected, that catalyzes the decomposition of **47**. This line of thought will be revisited in Chapter 6.

**Scheme 5.9**



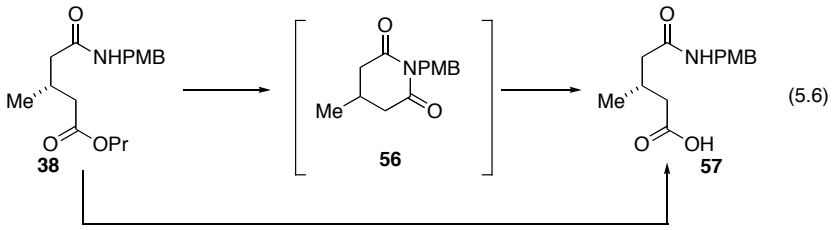

a) $HSbF_6 \cdot 6H_2O$, MeOH, $CH_2Cl_2$; b) **42c**, DCE, 40 °C

Concurrently to the efforts described above, Dr. Bidschädler and I had investigated the fesability of actually conducting the Diels–Alder reaction with a benzyl group or derivative in place, and subsequently removing it. We were ultimately unsuccessful at this, and it appeared that the reactivity problem was solved with the use of hexafluoroantimonate counterions. However, in chapter 6 it is disclosed that the proton on the iminium may be detrimental to the stereochemical course of the reaction. Had a

method of removing a substituent on the nitrogen been feasible, it would have been valuable. The attempted N-dealkylations were mainly conducted by Dr. Bindschädler. Attacks by nucleophiles on adducts such as **31** to effect an $S_N2$ reaction at the benzyl group were mainly thwarted by deprotonation at $C_{31}$ to form an enamine. Attempts to oxidatively remove a PMB group from the nitrogen at the iminium stage did not proceed, presumably due to the difficulty of oxidizing an aryl group with a neighbouring iminium cation attached. Oxidative removal of the PMB from the deprotonated enamine tautomer resulted in destruction of the enamine. The only partially successful debenzylation conditions involved hydrogenolysis of the benzyl group, but it was judged that such conditions would not be compatible with the disubstituted olefin at $C_{12}$-$C_{13}$ in spiro-prorocentrimine.

## VI. Revision of the Dienophile Synthesis

The dienophiles prepared by Dr. Bindschädler's route from compound **19** had provided very useful in the course of experiments to determine the mode of activation of the Diels–Alder reaction as described above. However, in later stages of the work on this project, a problem with the preparation of the dienophile was detected in a scale-up campaign. Notably, during the hydrolysis of the ester in compound **38**, signifigant quantites of very non polar intermediates were detected by TLC. The resultant products did not contain any of these impurities, and were very clean by $^1$H NMR analysis. It was hypothesized that during the hydrolysis, some achiral imide **56** was being formed, which could be anticipated to be much less polar than both the starting material and desired product (Equation 5.6). Since the intermediates prepared by Dr. Bindschädler were non-racemic (as evidenced by their optical rotation), intermediacy of the imide is not thought to be the sole pathway to produce the acid amide **57**.




(5.6)

It was decided to investigate a new route for scale up that precluded the possibility of the formation of achiral intermediates, and subsequent racemization. It was also decided to attempt to intercept the intermediates on the route to the dienophile that Dr. Bindschädler used, to minimize the amount of peturbation in the synthesis.

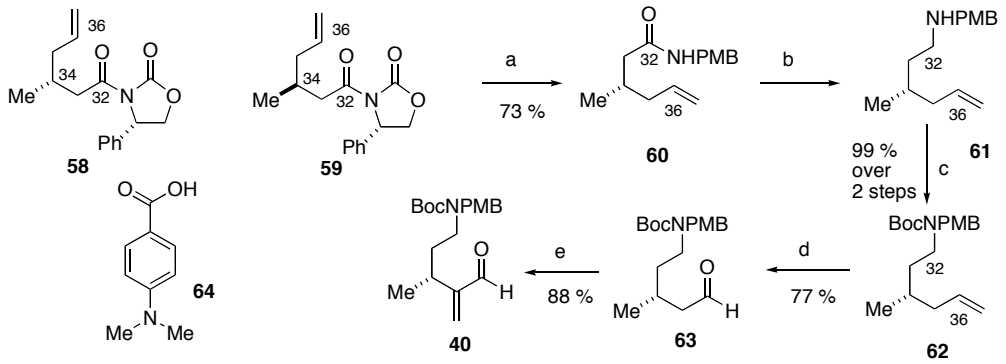
In Dr. Chiu's route, product **58** of a Sakurai addition to an oxazolidinone bearing a crotonate was used to set the initial stereocentre.[20] Rather than following her route, which necessitated the use of stoichiometric amounts of BOM chloride, and a sensitive reduction of an aldehyde in the presence of the ketone, a reversal of the ends in a diastereomeric conjugation allylation product was envisioned. In this case, the imide in compound **59** would be elaborated to a protected amine at $C_{36}$, while the allyl group would serve as an aldehyde surrogate at $C_{32}$ (Scheme 5.10). This also had the advantage that the use of the natural series of the oxazolidinone could be maintained by switching the Sakurai method of allylation to a conjugate addition of allylcopper as reported by Williams, which is documented to have the opposite stereochemical outcome.[21] Compound **59** is available in greater than 40: 1 dr, which is important since the diastereomers are not readily separated, and this ratio becomes the enantiomer ratio in the next step. PMB amide **60** was prepared by an $AlMe_3$ mediated transamidation of **59** with $PMBNH_2$. This amide could be cleanly reduced to amine **61** by the action of $LiAlH_4$ in THF. The amine is then protected to give Boc amide **62**, and ozonolysis reveals aldehyde

(20) Wu, M.-J.; Wu, C.-C.; Lee, P..-C. *Tetrahderon Lett.* **1992**, *33*, 2547-2548. Note that the stereochemistry of the Sakurai conjugate addition product in the above reference is misassigned. For the correct stereochemistry see: Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun*. **2003**, 2220-2221.

(21) Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett.* **1998**, *39*, 8593- 8596.

**62**. A Mannich reaction,[22] using modified conditions and aminobenzoic acid **64** provided enal **40**, which was identical to that prepared earlier in all respects except optical rotation.

**Scheme 5.10**



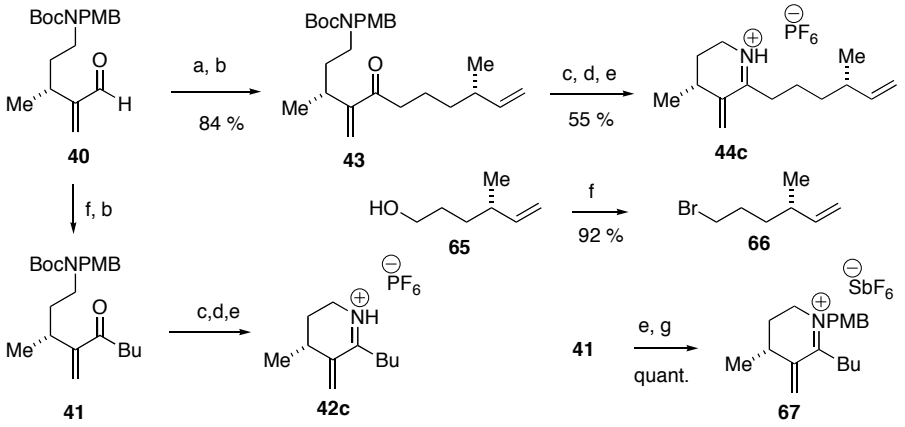

a) $PMBNH_2$, $AlMe_3$, tol/ $CH_2Cl_2$; b) $LiAlH_4$, THF, 66 °C; c) $Boc_2O$, $CH_3CN$, 40 °C; d) $O_3$, Sudan III, $CH_2Cl_2$ , -78 °C, then $PPh_3$; e) **64**, $C_4H_8NH$, $CH_2Cl_2$, **63**, $CH_2O_{(aq)}$.

This 5 step sequence intercepted enal **40** on the prior route, and favourably compares in step count. Comparison of optical rotations of the enal **40** prepared in both the current and previous route showed that the use of this sequence was justified, as the optical rotation measured for enal **40** was of the same sign, but over four times as much as that prepared from the enzymatic desymmetrization. Compound **40** was elaborated to both butyl containing model system **42c** and side chain containing iminium **44c** (Scheme 5.11). The hexafluorophosphates have very similar reactivity, properties and spectra to the hexafluoroantimonates, with the exception that the counterions can be observed by $^{19}F$ NMR. As explained in the next chapter, it became important to quantify the extent of counterion exchange, and antimony containing counterions do not have well behaved $^{19}F$ spectra. A more efficient method than alkyllithium addition was also employed to introduce the methyl-hexenyl side chain. Alcohol **65** was converted to bromide **66**. Examination of the literature showed that Mulzer had prepared a Grignard reagent of the corresponding bromide without observation of cyclization.[23]

(22) Erkkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538-2541.

(23) Martin, H. J.; Pojarliev, P.; Kählig, H.; Mulzer, J. *Chem. Eur. J.* **2001**, *7*, 2261- 2271.

**Scheme 5.11**




a) **66**, Mg, THF, then **40;** b) $SO_3$•py, *i*-$Pr_2NEt$, DMSO, $CH_2Cl_2$ 0 °C; c) CAN, $CH_3CN$/ $H_2O$ ; d) TFA, $CH_2Cl_2$; e) $KPF_{6(aq)}$, $CH_2Cl_2$; f) $PPh_3Br_2$, im, $CH_2Cl_2$ g) $HSbF_6$ •$6H_2O$, MeOH/ $CH_2Cl_2$ .

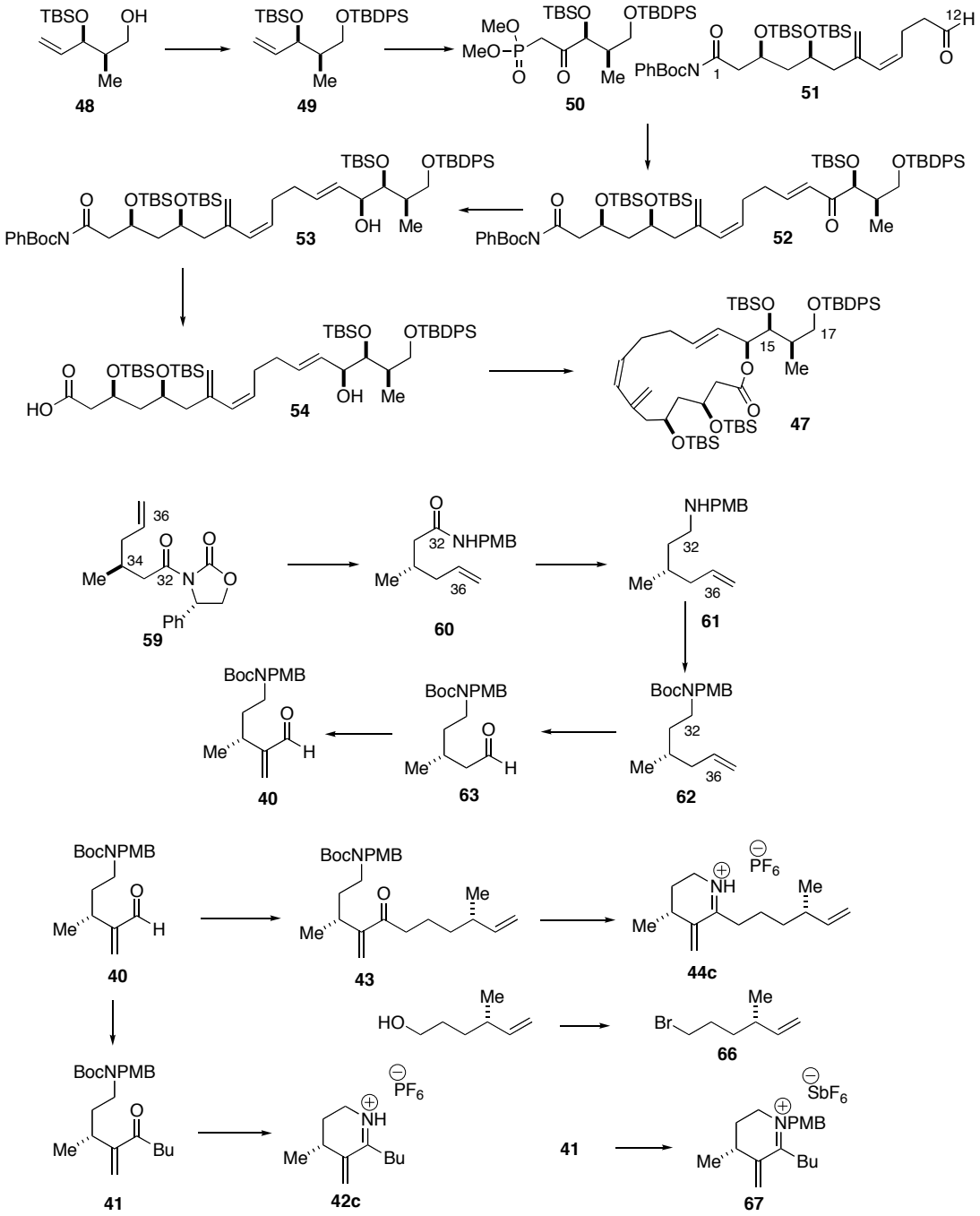
The desired Grignard reagent was prepared with a large excess of magnesium turnings entrained with 1 eq of magnesium bromide in THF. The addition of this side chain to the enal could be conducted on gram scale, at room temperature with only minor amounts of side products. The main side product that corresponded to a 1,2 reduction of the Enal (a common side reaction of Grignard additions to compounds that are able to form stabilized radicals). The new dienophile, of cetain stereochemical integrity was employed in the reactions described in the next chapter. Dienophile **67** could also be prepared from enone **41**.

**VII. Conclusion**

An efficient synthesis of several chiral iminium dienophiles allowing a higher material throughput than previous routes was developed in conjunction with Dr. Pascal Bindschadler. An even more efficient route was later developed which absolutely precluded stereochemical scrambling by removing the mechanistic possibility of forming *meso* intermediates. During the course of Diels–Alder reactions involving these iminium dienophiles it was observed that non-coordinating counterions resulted in faster Diels-Alder reactions than coordinating counterions. The success of the reactions of iminium dienophiles on macrocyclic dienes conducted by Dr. Joseph Pero is now attributed to this

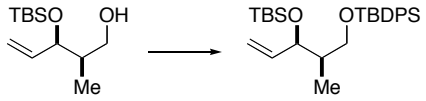
counterion effect rather than a rate acceleration provided by the more electronegative alkylation of the iminiums. Alkylated iminiums were shown to not be viable candidates for the construction of spiro-prorocentrimine as no reliable method could be found to effect dealkylation. A model system was synthesized to study the Diels–Alder reactions on *Z*-dienes without consuming expensive **3**.

## VIII. Graphical Summary



## IX. Experimental Section

### (5*R*,6*R*)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-5-vinyl-4,8-dioxa-3,9-disilaundecane (49)




**48** **49**

Alcohol **48** (910 mg, 3.94 mmol, 1 eq) was dissolved in 5 mL $CH_2Cl_2$ and imidazole (402 mg, 5.91 mmol, 1.5 eq) was added. The reaction was cooled to 0 °C and TBDPSCl (1.44 mL, 5.53 mmol, 1.4 eq) was added dropwise by syringe. A thick white precipitate immediately formed. TLC after 2 hours (5% EtOAc/hex, **48** is baseline and stains faint grey in CAM) showed complete consumption of **48**. The reaction was quenched by the addition of 1 mL of saturated $NH_4Cl_{(aq)}$ and diluted with 20 mL 90% hexanes/ EtOAc. This was washed with 5 mL of brine, then dried over $Na_2SO_4$, and concentrated *in vacuo*. . Purification by flash chromatography over silica gel (0.5% $Et_2O$/ Hexanes) afforded 1.8 g (3.86 mmol, 98%) of TBDPS ether **49** as a clear colourless oil.

$R_f$ = 0.80 (5% EtOAc/hexanes, UV active, stains blue CAM)

$[\alpha]^{20}_D$ = +1.8 (*c* 1.80, $CHCl_3$);

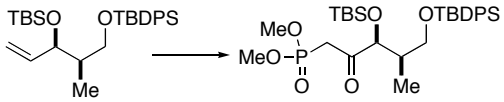
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.74- 7.71 (m, 4H), 7.49- 7.45 (m, 2H), 7.45- 7.41 (m, 4H), 5.85 (ddd, *J* = 16.9, 10.4, 6.1 Hz, 1H), 5.18 (dt, *J* = 16.9, 1.5 Hz, 1H), 5.09 (dt, *J* = 10.4, 1.1 Hz, 1H), 4.36 (ap. t, *J* = 5.1 Hz, 1H), 3.72 (AB dd, *J* = 10.0, 6.6 Hz, 1H), 3.54 (AB dd, *J* = 10.0, 6.2 Hz, 1H), 1.80- 1.73 (m, 1H), 1.11 (s, 9H), 0.93 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 140.7, 135.6 (broad signal), 134.0, 129.5, 127.6 (broad signal), 114.2, 73.6, 65.8, 42.4, 26.9, 25.9, 19.3, 18.2, 11.1, -4.2, -5.0

IR(film) 2957.3, 2857.5, 1472.0, 1427.8, 1251.6, 1112.2, 1074.8, 1027.9, 835.6 $cm^{-1}$;

Exact Mass Calc. for $C_{28}H_{44}O_2Si_2$ $[M + Na]^+$ : 491.27720 ; found : 491.27632 (ESI)

**dimethyl ((3*S*,4*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-2-oxopentyl)phosphonate (50)**




**49** **50**

Alkene **49** (680 mg, 1.45 mmol, 1 eq) was dissolved in 10 mL $CH_2Cl_2$ and cooled to -78 °C. Ozone was bubbled through the reaction until a blue colour persisted. The reaction was then sparged with nitrogen until the blue colour was discharged. Triphenylphosphine (380 mg, 1.45 mmol, 1 eq) was added and the cooling bath was removed. After 45 minutes, the volatiles were removed *in vacuo*, the residue was azeotroped with 2x 10 mL of benzene and the material was carried on crude to the next reaction.

TLC analysis of intermediate aldehyde:
$R_f$ = 0.75 (5 % EtOAc/hexanes, UV active, stains blue in CAM)

Dimethyl methyl phosphonate (0.775 mL, 7.25 mmol, 5.0 theory eq) was dissolved in 8 mL THF and cooled to -78 C. Freshly titrated nBuLi (3.16M in hexanes, 1.15 mL, 3.62 mmol, 2.5 eq) was added dropwise and the resulting clear colourless solution was stirred for 1 hour. After 1 hour, a solution of crude aldehyde in 5 mL THF was added dropwise

and the transfer was quantitated with an additional 2 mL THF. The reaction turned slightly tan in colour. After 15 minutes, TLC (20 % EtOAc/hexanes) showed complete consumption of the aldehyde, so the reaction was quenched with addition of 3 mL of saturated $NH_4Cl_{(aq)}$ and diluted with 20 mL 90% EtOAc/hexanes and 5 ml of water. The layers were separated and the aqueous layer was washed with 2 x 20 mL 90% EtOAc/hexanes. The combined organic extracts were washed with 5 mL of brine, then dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (75 % EtOAc/ Hexanes) afforded 600 mg ( 1.01 mmol, 69%) of an alcohol as a clear colourless oil and inconsequential mixture of diastereomers that was used immediately in the next step.

TLC analysis of intemediate alcohols:

$R_f$ = 0.15 (75% EtOAc/hexanes, UV active, stains purple in CAM)

The mixture of alcohols (600 mg, 1.01 mmol, 1 eq) was dissolved in 10 mL of $CH_2Cl_2$ that had been shaken with water in a separatory funnel. The solution was cooled to 0 °C and Dess–Martin periodinane (556 mg, 1.3 mmol, 1.3 eq) was added. The reaction immediately became turbid. After 1 hour, TLC showed complete consumption of starting material (50 % EtOAc/hex, product and SM visualize purple by CAM). To quench the reaction, 5 mL hexanes, 10 mL $CH_2Cl_2$, 10 mL saturated $NaHCO_{3(aq)}$ and 10 mL saturated $Na_2S_2O_{3(aq)}$ were added. The reaction was stirred until the biphasic layers were clear. The layers were separated and the aqueous layer was washed with 2 x 20 mL 90% EtOAc/hexanes. The combined organic extracts were washed with 10 mL of saturated $NaHCO_{3(aq)}$, then with 5 mL of brine, then dried over $Na_2SO_4$, and concentrated *in vacuo*. Purification by flash chromatography over silica gel (50 % EtOAc/ Hexanes) afforded 530 mg ( 0.892 mmol, 55% over 3 steps) of beta ketophosphonate **50** as a clear colourless oil.

$R_f$ = 0.50 (75% EtOAc/hexanes, UV active, stains blue-purple in CAM)

$[\alpha]^{20}_D$ = +16.7 (*c* 2.03, $CHCl_3$);

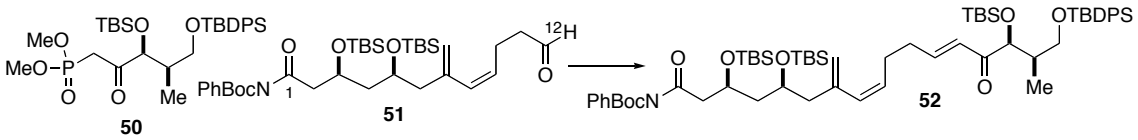
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.66 (ap. d, *J* = 7.0 Hz, 4H), 7.45- 7.41 (m, 2H), 7.39 (ap. t, *J* = 7.9 Hz, 4H), 3.78 (d, *J* = 5.2 Hz, 3H), 3.76 (d, *J* = 5.0 Hz, 3H), 3.59 (dd, *J* = 10.1, 8.5 Hz, 1H), 3.48 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.20 (dd, *J* = 21.8, 15.4 Hz, 1H), 3.01 (dd, *J* = 21.8, 15.4 Hz), 2.07- 2.00 (m, 1H), 1.07 (s, 9H), 0.90 (s, 9H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.07 (s, 3H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 203.8 (d, $^2J_{PC}$= 7.25 Hz), 135.5 (broad signal), 133.5, 129.7 (2 signals), 127.7 (broad signal), 77.9 (d, $^3J_{PC}$= 4.5 Hz), 65.1, 52.8 (broad signal), 39.2, 36.2 (d, $^1J_{PC}$= 134 Hz), 26.9, 25.8, 19.2, 18.2, 10.1, -4.7, -5.3;

IR(film) 2930.4, 2856.8, 1726.1, 1472.0, 1258.1, 1111.9, 1035.2 $cm^{-1}$;

Exact Mass Calc. for $C_{30}H_{49}O_6PSi_2$ $[M + Na]^+$ : 615.26975 ; found : 615.27141 (ESI)

**_tert_-butyl phenyl((3*S*,5*S*,8*Z*,12*E*,15*S*,16*R*)-3,5,15-tris((_tert_-butyldimethylsilyl)oxy)-17-((_tert_-butyldiphenylsilyl)oxy)-16-methyl-7-methylene-14-oxoheptadeca-8,12-dienoyl)carbamate**




Phosphonate **50** (640 mg, 0.969 mmol, 1.24 eq) was dissolved in 4 mL THF and cooled to 0 °C. To the reaction was added dropwise 3.16 M nBuLi in hexanes (0.284 mL, 0.897

mmol, 1.15 eq). The resulting mixture was stirred for 10 minutes, then aldehyde **51** (515 mg, 0.780 mmol, 1.0 eq) as a solution in 2 mL THF was added dropwise. The transfer was quantitated with a further 1 + 1 mL THF. The reaction was stirred for 15 hours, over which time it became turbid. TLC showed the reaction was not complete or progressing. The reaction was quenched with $NH_4Cl_{(aq)}$ and the aqueous layer was washed with 2 x 50 mL 90% EtOAc/hexanes. The combined organic layers were washed with brine, and dried over $Na_2SO_4$. Purification by flash chromatography (5% to 15% to 50% EtOAc/hexanes) allowed the recovery of 600 mg desired product **52** (0.533 mmol, 68%), 164 mg of recovered aldehyde **51** (0.248 mmol, 32%) and 260 mg of recovered phosphonate **50** (0.438 mmol, 45%). The recovered aldehyde and phosphonate were recycled under the same reaction conditions, and the desired project was combined with that from the prior reaction to yield a total of 790 mg (0.702 mmol, 90%) of enone **52** as a very viscous colourless oil.

$R_f$ = 0.55 (10% EtOAc/hexanes, strongly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -5.10 (*c* 2.05, $CHCl_3$);

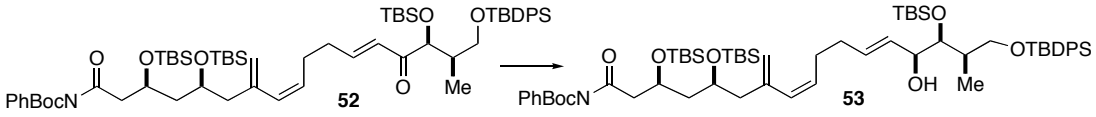
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 4H), 7.50- 7.42 (m, 8H), 7.39- 7.34 (m, 1H), 7.12 (ap. d, *J* = 7.3 Hz, 2H), 7.01 (dt, *J* = 15.7, 6.7, 1H), 6.53 (dd, *J* = 15.7, 1.3 Hz, 1H), 5.88 (d, *J* = 11.7 Hz, 1H), 5.54- 4.49 (m, 1H), 5.10 (s, 1H), 4.95 (s, 1H), 4.52 (ap. d, *J* = 3.2 Hz, 1H), 4.46 (ap. pentet, *J* = 4.8 Hz, 1H), 3.88 (ap. pentet, *J* = 6.0 Hz, 1H), 3.68 (t, *J* = 8.3, 1H), 3.51 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.16 (AB dd, *J* = 16.7, 7.3 Hz, 1H), 3.07 (AB dd, *J* = 16.7, 4.5 Hz, 1H), 2.45 (ap. q, *J* = 6.7, 2H), 2.38- 2.30 (m, 4H), 2.14- 2.06 (m, 1H), 1.75 (ap. t, *J* = 6.0 Hz, 2H), 1.42 (s, 9H), 1.13 (s, 9H), 0.97 (s, 9H), 0.94 (s, 9H), 0.94 (s, 9H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 6H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 201.7, 173.5, 152.6, 146.7, 141.6, 139.0, 135.6 (broad signal), 133.7 (2 signals), 131.1, 130.4, 129.6 (2 signals), 128.9, 128.3, 127.7, 127.6 (broad signal), 125.9, 116.2, 82.9, 76.7, 68.6, 66.7, 65.5, 45.8, 45.6, 45.1, 40.4, 33.0, 27.8, 27.3, 26.9, 26.0, 25.9, 25.8, 19.2, 18.2, 18.0 (2 signals), 10.4, -4.3, -4.4 (2 signals), -4.5, -4.6, -5.2;

IR(film) 2955.5, 2857.2, 1737.7, 1709.7, 1472.1, 1254.8, 1154.2, 1090.8, 836.8 $cm^{-1}$;

Exact Mass Calc. for $C_{64}H_{104}NO_8Si_4$ $[M + H]^+$ : 1126.6833 ; found : 1126.6472 (ESI)

**_tert_-butyl phenyl((3*S*,5*S*,8*Z*,12*E*,14*S*,15*S*,16*R*)-3,5,15-tris((_tert_-butyldimethylsilyl)oxy)-17-((_tert_-butyldiphenylsilyl)oxy)-14-hydroxy-16-methyl-7-methyleneheptadeca-8,12-dienoyl)carbamate (53)**




Enone **52** (570 mg, 0.506 mmol) was dissolved in 12 mL THF and 6 mL MeOH in a round bottom flask equipped with an internal thermocouple. To this mixture was added cerium trichloride heptahydrate (302 mg, 0.810 mmol, 1.6 eq) and the reaction was stirred until this dissolved. The reaction was cooled to an internal temperature of -60 °C and $NaBH_4$ was added as a solid. After 30 minutes TLC (10% EtOAc/Hexanes, Cam visualization) showed complete consumption of the starting material. The mixture was cooled to -78 °C and 0.2 mL of acetone was added dropwise. Saturated $NH_4Cl_{(aq)}$ was added and the reaction was rapidly diluted with 35 mL of a 85% EtOAc/Hexanes mixture. The bubbling mixture was shaken and washed with 10 mL saturated $NH_4Cl_{(aq)}$ and brine. This was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was taken

up in $CH_2Cl_2$, filtered through Celite® to remove any residual cerium salts and reconcentrated. The allylic alcohol **53** (570 mg, 0.506 mmol, quant.) was of sufficient purity to be used directly in the next step.

$R_f$ = 0.50 (10% EtOAc/hexanes, faintly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +1.6 (*c* 1.83, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.65 (ap. t, *J* = 7.9, 1.1 Hz, 4H), 7.44-7.39 (m, 2H), 7.39-7.34 (m, 6H), 7.31 (ap. t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 2H), 5.78 (d, *J* =11.5 Hz, 1H), 5.71 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.52- 5.44 (m, 2H), 5.02 (s, 1H), 4.92 (s, 1H), 4.43-4.39 (m, 1H), 4.00 (t, *J* = 6.1 Hz, 1H), 3.82 (sextet, *J* = 6.1 Hz, 1H), 3.77 (dd, *J* = 5.4, 3.2 Hz, 1H), 3.59 (AB dd, *J* = 10.1, 7.3 Hz, 1H), 3.53 (AB dd, *J* = 10.1, 6.1 Hz, 1H), 3.09 (AB dd, *J* = 16.7, 7.3 Hz, 1H), 2.89 (AB dd, *J* =16.7, 4.5 Hz, 1H), 2.52 (br. s, 1H), 2.38-2.27 (m, 2H), 2.25 (ap. t, *J* = 5.5 Hz, 2H), 2.14 (ap. q, *J* = 7.2 Hz, 2H), 1.86 (qd, *J* = 6.7, 3.1 Hz, 1H), 1.68 (t, *J* = 6.1 Hz, 2H), 1.36 (s, 9H), 1.05 (s, 9H), 0.88 (s, 18H), 0.87 (s, 9H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.5, 152.6, 141.7, 139.1, 135.6 (broad signal), 133.7, 133.6, 132.4, 131.5, 130.9, 130.4, 129.6, 128.9, 128.3, 127.7, 127.6 (broad signal), 116.1, 75.7, 73.7, 68.6, 66.8, 65.9, 46.0, 45.6, 45.0, 39.0, 32.8, 29.7, 28.4, 27.8, 26.9, 26.0 (2 signals), 25.9, 19.2, 18.3, 18.0, 11.4, -4.0, -4.4 (2 signals), -4.5;

IR(film) 3546.6, 2929.1, 2856.4, 1736.6, 1254.4, 1154.1, 1090.2, 835.8 $cm^{-1}$;

Exact Mass Calc. for $C_{64}H_{105}NO_8Si_4$ $[M + Na]^+$ : 1150.6810 ; found : 1150.6439 (ESI)

**(3*S*,5*S*,8*Z*,12*E*,14*S*,15*S*,16*R*)-3,5,15-tris((*tert*-butyldimethylsilyl)oxy)-17-((*tert*-butyldiphenylsilyl)oxy)-14-hydroxy-16-methyl-7-methyleneheptadeca-8,12-dienoic acid (54)**


Allylic alcohol **53** (560 mg, 0.496 mmol, 1 eq) was dissolved in 10 mL THF and cooled to -20 °C. To this solution was added 0.5 mL of 30 % aqueous hydrogen peroxide. To the homogenous solution was added 1 mL of 1 M $LiOH_{(aq)}$ (1 mmol, 2 eq) and 1 mL of deionized water. Crystals were observed to form which redissolved upon warming the reaction to 0 °C. The reaction was held at 0 °C for 18 hours at which time TLC showed complete consumption of starting material. The TLC analysis indicated the presence of both seco acid **54** and peracid (10% EtOAc/hexanes, CAM stain, $R_f$ sm=0.50, stains blue; $R_f$ BocAniline=0.47, stains yellow; $R_f$ Peracid = 0.45, stains blue; $R_f$ seco acid= 0.05, stains black ). To the solution at 0 °C are added 3 mL of saturated $Na_2SO_{3(aq)}$. After 5 minutes a KI/$KIO_3$/Starch peroxide test strip shows the absence of peroxides and TLC shows convergence of the peracid to the seco acid. The reaction was made acidic to pH paper by the addition of 1 M $NaHSO_4$. The reaction was diluted with 50 mL 95% EtOAc/hexanes and the aqueous layer was extracted with a further 50 mL of 95% EtOAc/hexanes. The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica (10% to 50% EtOAc/hexanes) yielded 430 mg of seco acid **54** (0.451 mmol, 91% over 2 steps) as a clear colourless very viscous oil.

$R_f$ = 0.3 (30% EtOAc/hexanes, UV active, stains black in CAM)

$[\alpha]^{20}_{D}$ = -9.6 (*c* 1.01, $CHCl_3$);

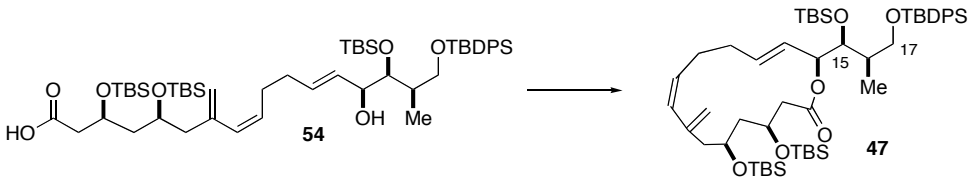
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.65 (ap. t, *J* = 6.6 Hz, 4H), 7.44- 7.39 (m, 2H), 7.39- 7.35 (m, 4H), 5.74 (d, *J* = 10.2 Hz, 1H), 5.73- 5.69 (m, 1H), 5.54- 5.44 (m, 2H), 5.02 (s, 1H), 4.93 (s, 1H), 4.32- 4.26 (m, 1H), 4.01 (t, *J* = 6.9 Hz, 1H), 3.80- 3.72 (m, 2H), 3.58 (AB dd, 10.3, 7.5 Hz, 1H), 3.53 (AB dd, 10.3, 6.2 Hz, 1H), 2.58 (AB dd, 15.2, 4.5 Hz, 1H), 2.42 (AB dd, 15.2, 6.0 Hz, 1H), 2.38 – 2.27 (m, 3H), 2.22- 2.12 (m, 3H), 1.89- 1.83 (m, 1H), 1.75- 1.68 (m, 1H), 1.68- 1.61 (m, 1H), 1.05 (s, 9H), 0.88 (s, 18H), 0.88 (s, 9H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 176.1, 141.1, 135.6 (broad signal), 133.7, 132.4, 131.9, 130.8, 130.0, 129.6 (2 signals), 127.6 (broad signal), 116.3, 75.6, 73.7, 68.5, 66.8, 65.9, 46.2, 44.1, 41.8, 40.0, 39.0, 32.8, 28.4, 26.9, 26.0, 25.9, 25.8, 19.2, 18.3, 17.9 (2 signals), 11.4, -4.1 (2 signals), -4.3, -4.4, -4.6, -4.9;

IR(film) 2955.0, 2856.9, 1713.0, 1471.8, 1254.5, 1106.5, 835.7 $cm^{-1}$;

Exact Mass Calc. for $C_{53}H_{92}O_7Si_4$ $[M - H]^-$ : 951.58473 ; found : 951.57660 (ESI)

**(*Z*) – TBDPS Truncated Model Macrocycle (47)**




DMAP (269 mg, 2.20 mmol, 5.0 eq) and 2-methyl-6-nitro-benzoic anhydride (378 mg, 1.10 mmol, 2.5 eq) were dissolved in 5 mL $CH_2Cl_2$ in a 100 mL round bottom flask under nitrogen. Separately seco acid **54** (420 mg, 0.440 mmol, 1 eq) was dissolved in 39 mL $CH_2Cl_2$ and added to the DMAP/ MNBA mixture by syringe pump at the rate of 3 mL/ hour. When the addition was complete, the reaction was stirred for a further 6 hours. The solvent was removed and the residue was purified by flash chromatography on silica (10% EtOAc/hexanes) to yield 405 mg of macrocycle **47** (0.433 mmol, 98%) as a very viscous clear colourless oil.

$R_f$= 0.85 (10 % EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -0.7 (*c* 1.13, $CHCl_3$);

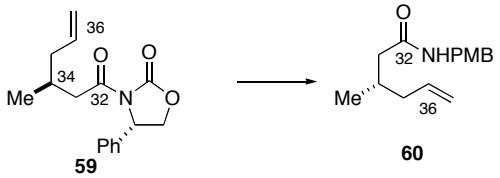
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.61 (m, 4H), 7.44- 7.40 (m, 2H), 7.40- 7.34 (m, 4H), 5.79 (d, *J* = 11.5 Hz, 1H), 5.56 (ap. pentet, *J* = 7.3 Hz, 1H), 5.39 (dd, *J* = 11.5, 6.1 Hz, 1H), 5.36- 5.31 (m, 1H), 5.03 (d, *J* = 2.0 Hz, 1H), 5.00 (dd, *J*= 8.4, 6.6 Hz, 1H), 4.84 (d, *J* = 1.8 Hz, 1H), 4.23- 4.14 (m, 2H), 4.03 (dd, *J* = 8.5, 1.3 Hz, 1H), 3.57 (t, *J* = 10.0 Hz, 1H), 3.36 (dd, *J* = 10.2, 6.1 Hz, 1H), 2.65 (AB dd, *J* = 14.2, 8.5, 1H), 2.47 (AB dd, *J* = 14.2, 3.3 Hz, 1H), 2.48- 2.43 (m, 1H), 2.35 (dd, *J* = 13.3, 3.6 Hz, 2H), 2.24- 2.14 (m, 3H), 1.75 (sextet, *J* = 7.3 Hz, 1H), 1.58- 1.51 (m, 2H), 1.47- 1.41 (m, 1H), 1.05 (s, 9H), 0.92 (s, 9H), 0.92 (s, 9H), 0.82 (s, 9H), 0.69 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 170.6, 141.3, 135.6 (broad signal), 133.9, 133.8, 133.1, 131.9, 131.1, 129.6, 129.5, 127.6 (broad signal), 127.0, 117.3, 77.1, 72.6, 67.4, 67.0, 66.0, 46.0, 43.1, 37.7, 32.5, 29.7, 28.4, 26.9, 26.1, 25.9, 25.8, 19.2, 18.3, 18.0 (2 signals), 9.3, -3.8 (2 signals), -4.5, -4.6, -4.7, -4.8;

IR(film) 2955.3, 2856.8, 1734.3, 1472.1, 1255.2, 1109.9, 836.2 $cm^{-1}$;

Exact Mass Calc. for $C_{53}H_{90}O_6Si_4$ $[M + Na]^+$ : 957.57067 ; found : 957.57151 (ESI)

**(*S*)-N-(4-methoxybenzyl)-3-methylhex-5-enamide (60)**




In a 500 mL flask equipped with a reflux condenser and the largest egg shaped stirbar that would fit through the neck, PMBM amine (5.63 mL, 43 mmol, 1.25 eq) was dissolved in 20 mL $CH_2Cl_2$. Trimethylaluminum (2.0 M in toluene, 20.7 mL, 41.4 mmol, 1.2 eq) was added dropwise through the reflux condenser. The resulting light yellow solution was stirred for 15 minutes, then a solution of the conjugate addition product **59** (9.43g, 34.5 mmol, 1 eq) in 30 mL $CH_2Cl_2$ was added. The transfer was quantitated with 2x 10 mL $CH_2Cl_2$. The reaction was stirred for 24 hours. TLC analysis (30% EtOAc/hex, starting material $R_f$= 0.55, visualizes light grey, product $R_f$= 0.20, visualized purple by CAM, **CAUTION:** TLC had extremely offensive odour and was kept in fumehood until cool) did not show complete consumption of starting material, but after this amount of time, baseline impurities were beginning to form. Water was allowed to flow through the reflux condenser, and the reaction was quenched by the cautious and dropwise addition of

60 mL of saturated aqueous Rochelle's salt solution. CAUTION: It should be noted a several second induction period was noted between the addition of the aqueous solution of Rochelle's salt and gas evolution, so the addition was done cautiously. After the addition of the Rochelle's salt solution was complete, an additional 120 mL of $CH_2Cl_2$ were added, and the reaction was vigorously stirred for 18 hours. The resulting biphasic mixture was filtered through a medium frit and the layers were separated. The aqueous layer was washed with 2 x 100 mL 90% EtOAc/hexanes. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. . Purification by flash chromatography over silica gel (30% to 50% EtOAc/ Hexanes) afforded 2.30g (8.41 mmol, 24%) of recovered starting material **59** as a white crystalline solid. The desired product was obtained as a white crystalline solid (4.95g, 20.0 mmol, 58% ). The recovered starting material was recycled under the same stoichiometry and combined with amide **60** (overall yield, 6.26g, 25.3 mmol, 73%). It should be noted that the recovery of oxazolidine from this reaction was less than 30% in smaller batches, and in practice was not performed on this scale.

$R_f$ = 0.20 (30% EtOAc/hexanes, UV active, stains purple in CAM, **CAUTION:** TLC is accompanied by extremely offensive smell)

$[\alpha]^{20}_D$ = -4.8 (*c* 0.80, $CHCl_3$);

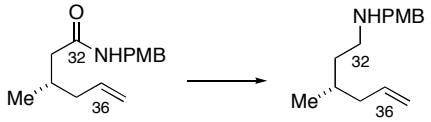
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.20 (ap. d, *J* = 6.3 Hz, 2H), 6.86 (ap. d, *J* = 6.3 Hz, 2H), 5.81- 5.73 (m, 1H), 5.60 (br. s, 1H), 5.03- 5.00 (m, 1H), 4.99 (ap. d, *J* = 5.4 Hz, 1H), 4.40- 4.35 (m, 2H), 3.80 (s, 3H), 2.22 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.15- 2.06 (m, 2H), 2.15- 2.06 (m, 2H), 1.95 (dd, *J* = 13.9, 7.8 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 172.0, 159.0, 136.5, 130.5, 129.2, 116.5, 114.0, 55.3, 43.6, 43.0, 41.0, 30.5, 19.5;

IR(film) 3257.5, 3072.8, 2957.9, 1637.0, 1544.4, 1513.6, 1458.6, 1248.6, 1028.5 $cm^{-1}$;

Exact Mass Calc. for $C_{15}H_{21}NO_2$ $[M + H]^+$ : 248.1645 ; found : 248.1647 (ESI)

**(*S*)-N-(4-methoxybenzyl)-3-methylhex-5-en-1-amine (61)**




**60** **61**

Lithium aluminum hydride (1.37g, 36.1 mmol, 2.0 eq) was placed in a 500 mL flask equipped with an egg shaped stir bar and a reflux condenser under nitrogen. The lithium aluminum hydride was suspended in 10 mL of THF, and amide **60**, dissolved in 20 mL THF was added dropwise with a needle and syringe, with considerable gas evolution. The transfer was quantitated using 6 mL of THF. The solution was heated to reflux, and held at that temperature for 9 hours. The reaction was removed from the heating bath, allowed to cool until bubbling just stopped. A solution of 1g of KOH in 4.5 mL $H_2O$ was added through the reflux condenser with great caution. **CAUTION:** it is imperative that the work-up be done drop-wise with extreme caution due to an exotherm in a solution near its boiling point. Doing the work-up on a cooler reaction results in poor granulation and a much inferior yield on work-up. After the addition of the KOH solution, the reaction was returned to the heating bath and allowed to reflux for another 15 minutes. The reaction was then poured hot through a pad of Celite®, and the granular white suspension was rinsed with 100 mL of EtOAc. Concentration yielded amine **61** as a clear colourless oil. No further purification was required. Due to the volatile nature of the amine, EtOAc was

not completely removed from the bulk sample using high vacuum, but an aliquot was freed of EtOAc for characterization by exposure to high vacuum for 5 hours.

$R_f$ = 0.1 (streaks, 30% EtOAc/hexanes, not UV active, stains in cold $KMnO_4$)

$[\alpha]^{20}_D$ = -3.0 (*c* 0.70, $CHCl_3$);

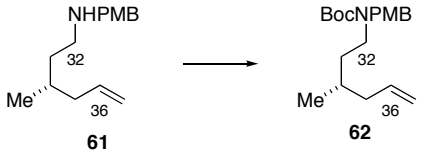
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.23 (ap. d, *J* = 8.2 Hz, 2H), 6.87 (ap. d, *J* = 8.2 Hz, 2H), 5.77 (ap. sextet, *J* = 4.7 Hz, 1H), 4.99 (ap. d, *J* = 7.7 Hz, 1H), 4.97 (s, 1H), 3.80 (s, 3H), 3.72 (s, 2H), 2.70 – 2.58 (m, 2H), 2.09- 2.03 (m, 1H), 1.93- 1.87 (m, 1H), 1.62- 1.52 (m, 2H), 1.37- 1.29 (m, 1H), 0.88 (d, *J* = 6.1

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.5, 137.3, 132.7, 129.2, 115.7, 113.7, 55.2, 53.5, 47.3, 41.5, 36.8, 30.9, 19.5;

IR(film) 2954.3, 2834.2, 1612.0, 1512.4, 1461.5, 1300.7, 1246.7, 1174.0, 1105.6, 1037.6, 911.1, 821.1 $cm^{-1}$;

Exact Mass Calc. for $C_{15}H_{23}NO$ $[M + H]^+$ : 234.1852 ; found : 234.1840 (ESI)

**(*S*)-*tert*-butyl 4-methoxybenzyl(3-methylhex-5-en-1-yl)carbamate (62)**




The crude amine **61** was dissolved in 36 mL $CH_3CN$ in a 250 mL RBF equipped with an egg shaped stir bar. $Boc_2O$ (3.9g, 18 mmol, 1.0 theory eq.) was added. The flask, open to air was immersed in an oil bath preheated to 40 °C. Bubbling commenced immediately. After 1 hour, volatiles were removed in vacuo and the residue was purified by flash

chromatography on silica (6% EtOAc/hexanes). Boc amide **62** (5.94 g, 99% over 2 steps) was obtained as a clear colourless oil. Rotamers were observed in a wide variety of NMR solvents, but $CD_3CN$ proved ideal for characterization.

$R_f$ = 0.55 (20% EtOAc/hexanes, faintly UV active, stains in $KMnO_4$ when heated)

$[\alpha]^{20}_D$ = +1.9 (*c* 2.1, $CHCl_3$);

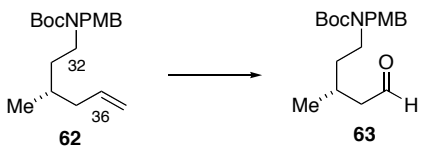
$^1$H NMR (600 MHz, $CD_3CN$) δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.78-5.69 (m, 1H), 5.00- 4.91 (m, 2H), 4.31 (br. s, 2H), 3.76 (s, 3H), 3.13 (br. s, 2H), 2.01 (br. s, 1H), 1.91- 1.84 (m, 2H), 1.53- 1.46 (m, 1H), 1.43 (br. s, 9H), 1.28- 1.20 (m, 1H), 0.84 (d, *J* = 6.6 Hz, 3H);

$^{13}$C NMR (125 MHz, $CD_3CN$) δ 159.8, 156.6 (broad signal), 138.3, 132.0, 129.7, 116.27, 114.7, 79.8, 55.8, 50.2 (broad signal), 45.2 (broad signal), 41.8, 35.1 (broad signal), 31.3, 28.6, 19.7;

IR(film) 2973.3, 2928.6 1693.3, 1513.2, 1247.6, 1171.2 $cm^{-1}$;

Exact Mass Calc. for $C_{20}H_{31}NO_3$ $[M + Na]^+$ : 356.21961 ; found : 356.2219 (ESI)

**(*R*)-*tert*-butyl 4-methoxybenzyl(3-methyl-5-oxopentyl)carbamate (63)**




**62** **63**

Alkene **62** (3.77g, 11.3 mmol 1 eq) was dissolved in 38 mL $CH_2Cl_2$ in a 100 mL flask. A pipette tip of Sudan III dye was added. The red mixture was cooled to -78 °C and sparged with ozone until the colour of the mixture faded to a peach colour. The reaction mixture

was sparged with nitrogen for one minute. Triphenylphosphine (2.96g, 11.3 mmol, 1 eq) was added, and the cooling bath was removed. The reaction mixture was stirred under nitrogen for 2 hours, then the solvent was removed in vacuo and the residue was purified by flash chromatography on silica (10% EtOAc/hexanes to 30% EtOAc/hexanes). Aldehyde **63** (2.92g, 8.70 mmol, 77%) was obtained as a pink viscous oil (the aldehyde co-elutes with a residue from the Sudan III dye which is not detrimental to the subsequent reaction.)

$R_f$ = 0.50 (20% EtOAc/hexanes, faintly UV active, stains in $KMnO_4$ when heated)

$[\alpha]^{20}_D$ = +11.6 (*c* 4.14, $CHCl_3$);

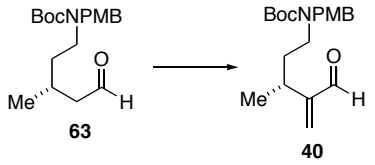
$^1$H NMR (600 MHz, $CD_3CN$) δ 9.62 (br. s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.31 (br. s, 2H), 3.76 (s, 3H), 3.15 (br. s, 3H), 2.43- 2.29 (m, 1H), 2.23- 2.14 (m, 1H), 1.52- 1.30 (m, 12H), 0.89 (d, *J* = 6.7 Hz, 3H);

$^{13}$C NMR (125 MHz, $CD_3CN$) δ 203.8, 159.8, 156.5 (broad signal), 131.9, 129.8, 114.7, 80.0, 55.8, 51.2, 49.8 (broad signal), 45.1 (broad signal), 35.7 (broad signal), 28.6, 26.4, 20.1;

IR(film) 2931.3, 1724.1, 1689.8, 1513.3, 1464.1, 1413.2, 1354.4, 1247.7, 1170.0 $cm^{-1}$;

Exact Mass Calc. for $C_{19}H_{29}NO_4$ $[M + Na]^+$ : 358.19888 ; found : 358.2014 (ESI)

**(*R*)-*tert*-butyl (4-formyl-3-methylpent-4-en-1-yl)(4-methoxybenzyl)carbamate (40)**




Aldehyde **63** (2.92g, 8.70 mmol, 1 eq) was dissolved in 22 mL $CH_2Cl_2$ in a 100 mL flask equipped with the largest football shaped stirbar that would fit. To the resulting solution was added 3.5 mL of a 37 wt % aqueous solution of formaldehyde (43 mmol, 5.0 eq). Para-dimethylaminobenzoic acid (0.718g, 4.35 mmol, 0.5 eq) was added, followed by pyrrolidine (0.363 mL, 4.35 mmol, 0.5 eq). Upon the addition of pyrrolidine, the PDABA went into solution. The biphasic solution was stirred vigorously under air for 4 hours (disappearance of the starting material by TLC is rapid, but full conversion to the Mannich product requires additional time). The reaction was quenched by the addition of 10 mL of a 1 M aqueous solution of citric acid, and the layers were separated. The aqueous layer was washed with 2 x 50 mL $CH_2Cl_2$ and the combined organic layers were washed with brine. A suspension of para-dimethylaminobenzoic acid is carried in the organic layer through these steps, but is not detrimental to the product upon concentration. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica (20 % EtOAc/ hexanes) to yield 2.69g of enal **40** (7.63 mmol, 88%) as a thick pale yellow oil.

$R_f$ = 0.45 (20% EtOAc/hexanes, strongly UV active, stains in cold $KMnO_4$)

$[\alpha]^{20}_D$ = -4.5 (*c* 2.18, $CHCl_3$);

$^1$H NMR (600 MHz, $CD_3CN$) δ 9.48 (s, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.28 (br. s, 1H), 6.04 (s, 1H), 4.36- 4.29 (m, 1H), 4.24 (AB d, *J* = 5.4 Hz, 1H),

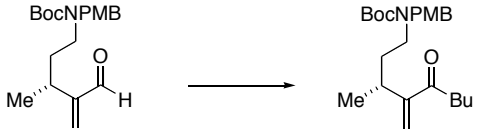
3.74 (s, 3H), 3.14- 2.93 (m, 2H), 2.56 (q, $J$ = 6.7 Hz, 1H), 1.69- 1.63 (m, 1H), 1.55- 1.48 (m, 1H), 1.42 (br. s, 9H), 1.01 (d, $J$ = 7.0 Hz, 3H);

$^{13}$C NMR (125 MHz, $CD_3CN$) δ 195.6, 159.8, 156.1, 155.6, 134.2, 131.9, 129.8, 114.7, 79.9, 55.8, 50.0 (broad signal), 45.3 (broad signal), 34.0 (broad signal), 29.8, 28.6, 20.0;

IR(film) 2972.3, 1693.9, 1612.7, 1513.5, 1463.5, 1413.5, 1365.7, 1247.6, 1169.3, 1035.7, 949.5, 883.1 cm$^{-1}$;

Exact Mass Calc. for $C_{20}H_{29}NO_4$ $[M + Na]^+$ : 370.1989 ; found : 270.2015 (ESI)

**(*R*)-*tert*-butyl 4-methoxybenzyl(3-methyl-4-methylene-5-oxononyl)carbamate (41)**




Enal **40** (901 mg, 2.59 mmol, 1 eq) was dissolved in 8.6 mL THF and cooled to -78 °C under nitrogen. To this solution was added a 3.3 M solution of nBuLi in hexanes (0.864 mL, 2.84 mmol, 1.1 eq). Upon completion of the addition of one equivalent, a bright yellow colour formed. TLC (20% EtOAc/hexanes, $KMnO_4$ visualization) shows complete consumption of the starting material. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ and extracted using $CH_2Cl_2$. The combined organic layers were washed with brine and dried over $Na_2SO_4$. The resulting oil was azeotroped with benzene and used directly in the next step. The azeotroped oil was dissolved in 8.6 mL DCM and cooled to 0 °C. To this mixture was added Hunig's base (1.4 mL, 7.8 mmol, 3.0 theoretical eq.) and DMSO (1.1 mL, 15 mmol, 6.0 theoretical eq.). $SO_3$-Py (824 mg, 5.2 mmol, 2.0 theoretical eq.) was added as a solid and the reaction mixture was stirred until TLC showed complete consumption of the diastereomeric alcohols (20% EtOAc/hex, $KMnO_4$

visualization). The volatiles were removed *in vacuo* and the residue was purified by flash chromatography to yield 765 mg of enone **41** (1.89 mmol, 73% yield over 2 steps).

Rf = 0.50 (20% EtOAc/hexanes, strongly UV active, stains in cold $KMnO_4$)

$[\alpha]^{20}_D$ = -4.5 (*c* 2.16, $CHCl_3$);

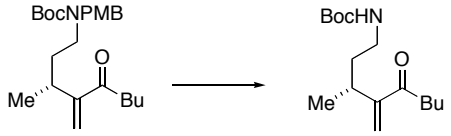
$^1$H NMR (600 MHz, $CD_3CN$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.05 (s, 1H), 5.70 (s, 1H), 4.35- 4.28 (m, 1H), 4.24 (AB d, *J* = 15.4 Hz, 1H), 3.75 (s, 3H), 3.10- 2.91 (m, 2H), 1.93 (pentet, *J* = 2.5 Hz, 2H), 1.58 (ap. septet, *J* = 6.6 Hz, 1H), 1.50 (pentet, *J* = 7.6 Hz, 2H), 1.42 (br. s, 9H), 1.32- 1.25 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.6 Hz, 3H);

$^{13}$C NMR (125 MHz, $CD_3CN$) δ 203.0, 159.8, 156.0 (broad signal), 154.3, 131.9, 129.8, 122.9, 114.7, 79.9, 55.8, 49.7 (broad signal), 45.5 (broad signal), 38.5, 35.2 (broad signal), 31.5, 28.6, 27.6, 26.9, 23.1, 20.6, 14.2;

IR(film) 2860.4, 1872.4, 1691.4, 1612.8, 1513.2, 1463.9, 1412.7, 1365.5, 1302.3, 1247.9, 1169.5, 1036.0 $cm^{-1}$;

Exact Mass Calc. for $C_{24}H_{37}NO_4$ $[M + Na]^+$ : 426.2615 ; found : 426.2609 (ESI)

**(*R*)-*tert*-butyl (3-methyl-4-methylene-5-oxononyl)carbamate (S1)**




**41** **S1**

PMB amide **41** (502 mg, 1.24 mmol, 1 eq) was dissolved in 10 mL $CH_3CN$ at ambient temperature. To the stirring solution was added 1 mL $H_2O$, then CAN (1.7 g, 3.1 mmol, 2.5 eq). The cloudy orange solution was stirred for 1.5 hours, until TLC (20% EtOAc/hexanes) showed complete consumption of starting material. The reaction was diluted with 60 mL 90% EtOAc/hexanes and washed with 2x 10 mL saturated $NH_4Cl_{(aq)}$. The aqueous layers were extracted with 50 mL 90 % EtOAc/hexanes. The combined organic layers were washed with brine, then dried over $Na_2SO_4$. Concentration *in vacuo* yielded a chalky yellow residue that was purified by flash chromatography (5% EtOAc/hexanes, it should be noted the order of elution of anisaldehyde and product is opposite that shown on the TLC, with anisaldehyde eluting first from the column). The product Boc amide **S1** , (180 mg, 0.635 mmol, 51% was obtained as a clear colourless oil.

Rf = 0.40 (20% EtOAc/hexanes, weakly UV active, stains in cold $KMnO_4$)

$[\alpha]^{20}_D$ = -22.1 (*c* 1.57, $CHCl_3$);

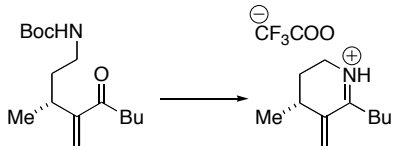
$^1$H NMR (600 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.75 (s, 1H), 4.72 (br. s, 1H), 3.17- 3.11 (m, 1H), 2.95 (ap. septet, *J* = 5.8 Hz, 1H), 2.86 (ap. sextet, *J* = 7.5 Hz, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 1.62- 1.51 (m, 4H), 1.43 (br. s, 9H), 1.34 (sextet, *J* = 7.3 Hz, 2H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 202.6, 155.9, 153.4, 122.7, 78.9, 38.5, 37.8, 36.8, 30.1, 28.4, 26.8, 22.4, 20.1, 13.9;

IR(film) 3389.8, 2961.6, 2932.5, 1713.9, 1704.2, 1694.0, 1514.6, 1366.1, 1249.5, 1173.3 $cm^{-1}$;

Exact Mass Calc. for $C_{16}H_{29}NO_3$ $[M + Na]^+$ : 306.2039 ; found : 306.2039 (ESI)

**(*R*)-6-butyl-4-methyl-5-methylene-2,3,4,5-tetrahydropyridin-1-ium 2,2,2-trifluoroacetate (42a)**



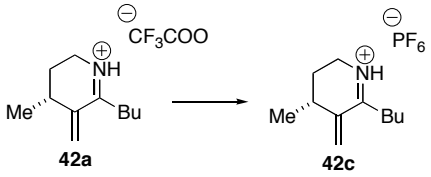

Boc amide **S1** (180 mg, 0.635 mmol, 1 eq) was dissolved in 1 mL $CH_2Cl_2$ and 1 mL TFA was added. After 5 minutes at ambient temperature, the volatiles were removed, and the yellowish residue was azeotroped 2x 5 mL $CH_2Cl_2$. The residue was taken up in 5 mL $CHCl_3$ and refluxed for 1 hour. Removal of volatiles *in vacuo* yielded 273 mg of TFA iminium **42a** as a brownish oil. Estimation of the yield was complicated by the presence of approximately 2 equivalents of TFA that could not be removed despite extensive pumping.

Partial Characterization Data (Proton NMR):

$^1$H NMR (600 MHz, $CDCl_3$) δ 13.62- 13.27 (broad bump, 1H), 6.35 (s, 1H), 6.16 (s, 1H), 3.90 – 3.83 (m, 1H), 3.83- 3.76 (m, 1H), 2.93- 2.86 (m, 2H), 2.72- 2.66 (m, 1H), 2.11-2.05 (m, 1H), 1.78- 1.70 (m, 1H), 1.65 (pentet, $J$ = 8.2 Hz, 2H), 1.41 (ap. sextet, $J$ = 6.9 Hz, 2H), 1.27 (d, $J$ = 6.9 Hz, 3H), 0.94 (t, $J$ = 7.3 Hz, 3H);

Exact Mass Calc. for $C_{20}H_{29}NO_4$ $[M + Na]^+$ : 370.1989 ; found : 270.2015 (ESI)

**(*R*)-6-butyl-4-methyl-5-methylene-2,3,4,5-tetrahydropyridin-1-ium hexafluorophosphate(V) (42c)**




The TFA iminium **42a** / TFA mixture (100 mg, 0.232 mmol based on 100% yield for preceding step) was dissolved in 5 mL $CH_2Cl_2$. A solution of $KPF_6$ (650 mg, 3.58 mmol, 15 eq) was dissolved in 3 mL water and the two solutions were mixed vigorously with a pipette in a test-tube for 2 minutes. The organic layer was removed with a pipette and the aqueous layer was washed with a further 5 mL $CH_2Cl_2$. The organic layers were dried over $Na_2SO_4$ and the solvent was removed *in vacuo* to yield iminium hexafluorophosphate **42c** (70.3 mg, 0.226 mmol, 97% ) as a greasy solid melting at around ambient temperature. Analysis by $^{19}F$ NMR indicated removal of the trifluoroacetic acid, and greater than 95% conversion to the $PF_6$ salt. This compound was not > 95 % pure by NMR, but attempts at chromatography did not improve the quality of the material, and what was obtained was satisfactory for subsequent steps.

$R_f$ = 0.3 (10% MeOH/ $CH_2Cl_2$, strongly UV active, stains white/yellow in CAM)

$[\alpha]^{20}_D$ = +15.7 (*c* 1.71, $CHCl_3$);

$^1H$ NMR (600 MHz, $CDCl_3$) δ 11.30- 10.95 (broad bump, 1H), 6.41 (s, 1H), 6.19 (s, 1H), 3.96 – 3.84 (m, 2H), 2.92- 2.88 (m, 2H), 2.74- 2.67 (m, 1H), 2.13- 2.07 (m, 1H), 1.80- 1.73 (m, 1H), 1.68 (pentet, *J* = 7.9 Hz, 2H), 1.44 (ap. sextet, *J* = 7.6 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 181.6, 140.0, 132.8, 44.3, 34.0, 30.3, 30.0, 27.1, 22.4, 18.5, 13.4;

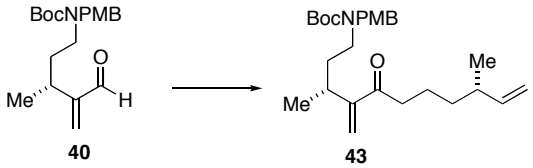
IR(film) 3651.6, 333.3, 2920.1, 1655.3, 1459.6, 968.5, 8400.9 $cm^{-1}$;

Exact Mass Calc. for $C_{11}H_{20}N$ $[M]^+$ : 166.1590 ; found : 166.1530 (ESI)

**(*S*)-6-bromo-3-methylhex-1-ene (66)**


Alcohol **65** (1.62g, 14.2 mmol, 1.0 eq) was dissolved in 47 mL $CH_2Cl_2$ and imidazole (1.16g, 17.0 mmol, 1.20 eq.) was added. The mixture was cooled to 0 °C and triphenylphosphine dibromide (6.59g, 15.6 mmol, 1.1 eq) was added. The reaction was stirred at 0 °C for 10 minutes, then the cooling bath was removed, and the reaction was stirred for an hour. TLC (10% EtOAc/hexanes, $KMnO_4$) showed complete consumption of starting material. The solvent was removed at 200 torr and the residue was purified by flash chromatography (pure pentane). The product containing fractions were concentrated at 250 torr, and the residue was briefly held at 150 torr to yield 2.31 g of bromide **66** (13.0 mmol, 92%) as a clear colourless oil. Spectral data were in accordance with the literature.[10]

***tert*-butyl ((3*R*,9*S*)-3,9-dimethyl-4-methylene-5-oxoundec-10-en-1-yl)(4-methoxybenzyl)carbamate (43)**




Enal **40** (2.65g, 7.63 mmol) was azeotroped with benzene and held under vacuum. Meanwhile a 3 neck flask equipped with a water cooled reflux condenser was flame dried

and cooled under argon. To the flask were added 2.46 g magnesium turnings (125 mmol, 17.0 eq) which were vigorously stirred under argon for 2 hours. THF (4 mL) was added to the turnings, and 0.150 mL 1,2-dibromoethane was added. A vigorous reaction ensued almost immediately. A solution of bromide **66** (2.21g, 12.5 mmol, 1.6 eq) in 4 mL THF was added at a rate sufficient to maintain reflux (approximately 10 minutes for complete addition). Alternating addition of 0.420 mL 1,2-dibromoethane (6.67 mmol total, 0.87 eq) was also performed to continually activate the magnesium. An additional 7 mL THF was added, and the grey solution was stirred and allowed to cool for 0.5 hours. Upon cooling, a grey precipate, assumed to be $MgBr_2$ formed. The enal was dissolved in 5 mL THF and cooled to -78 °C under argon. The Grignard reagent was transferred to the enal by syringe, with washing of the magnesium turnings with an additional 6 + 5 mL THF. A substantial amount of the $MgBr_2$ suspension remained in the flask. After 10 minutes, the Grignard reaction was warmed to 0 °C. TLC (20% EtOAc/hexanes , $KMnO_4$) showed complete consumption of the enal. The reaction was quenched with 10 mL saturated $NH_4Cl_{(aq)}$ and extracted with 3 x 50 mL (90% EtOAc/hexanes). The organic layers were washed with brine and dried over $Na_2SO_4$. Concentration yielded 3.4 g of a viscous oil that was used directly in the next step. The resulting oil was azeotroped with benzene and dissolved in 25 mL $CH_2Cl_2$ and cooled to 0 °C. To this mixture was added Hunig's base (4.10 mL, 22.9 mmol, 3.0 theoretical eq.) and DMSO (3.25 mL, 45.8 mmol, 6.0 theoretical eq.). $SO_3$-Py (2.43 g, 15.3 mmol, 2.0 theoretical eq.) was added as a solid and the reaction mixture was stirred until TLC showed complete consumption of the diastereomeric alcohols (20% EtOAc/hexanes, $KMnO_4$ visualization). The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (10% EtOAc/ hexanes) to yield 2.85 g of enone **43** (6.40 mmol, 84% yield over 2 steps). Eluting after the desired product were 300 mg of enal **40** contaminated with pyridine. Since the enal was completely consumed in the Grignard reaction it is believed this was the result of a

1,2 reduction of the enal by the Grignard, followed by reoxidation of the allylic alcohol in the Parikh–Doering reaction.

$R_f$ = 0.55 (20% EtOAc/hexanes, strongly UV active, decolourizes cold $KMnO_4$)

$[\alpha]^{20}_D$ = 2.6 (*c* 2.6, $CHCl_3$);

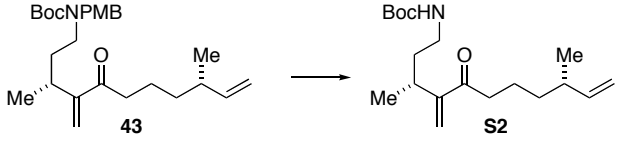
$^1$H NMR (500 MHz, $CD_3CN$) δ 7.17 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.07 (s, 1H), 5.77- 5.68 (m, 1H), 5.73 (s, 1H), 5.00 (ap. d, *J* = 17.1 Hz, 1H), 4.94 (ap. d, *J* = 10.2 Hz, 1H), 4.42- 4.31 (m, 1H), 4.27 (AB d, *J* = 15.6 Hz, 1H), 3.78 (s, 3H), 3.20- 3.91 (m, 2H), 2.73- 2.64 (m, 3H), 2.17- 2.08 (m, 2H), 1.66- 1.48 (m, 3H), 1.46 (br. s, 9H), 1.33 (ap. q, *J* = 7.3 Hz, 1H), 1.00 (d, *J* = 4.4 Hz, 3H), 0.99 (d, *J* = 4.5 Hz, 3H);

$^{13}$C NMR (125 MHz, $CD_3CN$) δ 202.9, 159.8, 156.0 (broad signal), 154.3, 145.6, 131.9, 129.8, 122.9, 118.2, 113.2, 79.9, 55.8, 50.0 (broad signal), 45.6, 38.7, 38.5, 36.8, 35.1 (broad signal), 31.5, 28.6, 23.2, 20.6;

IR(film) 2931.1, 1691.4, 1612.4, 1513.1, 1461.3, 1412.6, 1365.5, 1302.2, 1247.8, 1169.8, 1036.6, 910.3 $cm^{-1}$;

Exact Mass Calc. for $C_{27}H_{41}NO_4$ $[M + Na]^+$ : 466.2928 ; found : 466.2905 (ESI)

***tert*-butyl ((3*R*,9*S*)-3,9-dimethyl-4-methylene-5-oxoundec-10-en-1-yl)carbamate (S2)**



PMB amide **43** (970 mg, 2.19 mmol, 1 eq) was dissolved in 20 mL $CH_3CN$ and 2 mL $H_2O$ were added. To the mixture was added CAN (3.0g, 5.5 mmol, 2.5 eq) and the resulting orange mixture was stirred for 1 hour until TLC (20 % EtOAc/hexanes, product Rf= 0.53, anisaldehyde Rf= 0.50), showed complete consumption of starting material. The reaction was diluted with 100 mL 90% EtOAc/ hexanes and washed with 3 x 10 ml saturated $NH_4Cl_{(aq)}$, then brine. The organic layer was dried over $Na_2SO_4$ and filtered, then concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc/hexanes, the anisaldehyde elutes first, despite the order of elution on TLC) to yield 388 mg of BOC amide **S2** (1.20 mmol, 55%) as a clear colourless oil.

$R_f$ = 0.53 (20% EtOAc/hexanes, faintly UV active, stains in cold $KMnO_4$)

$[\alpha]^{20}_D$ = -12.1 (*c* 3.44, $CHCl_3$);

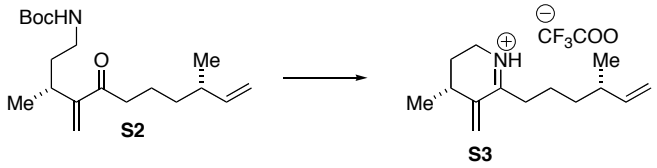
$^1$H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.47 (s, 1H), 5.72- 5.64 (m, 1H), 4.97 (ap. d, *J* = 17.1 Hz, 1H), 4.92 (ap.d, *J* = 10.2 Hz, 1H), 4.71 (br. s, 1H), 3.14- 3.09 (m, 1H), 2.96 (sextet, *J* = 6.9 Hz, 1H), 2.85 (sextet, *J* = 5.9 Hz, 1H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.13 (pentet, *J* = 7.3 Hz, 1H), 1.64- 1.58 (m, 2H), 1.57- 1.49 (m, 2H), 1.43 (br. s, 9H), 1.30 (ap. q, *J* = 6.9 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 202.4, 155.9, 153.3, 144.3, 122.8, 112.7, 78.9, 38.5, 38.0, 37.7, 36.7, 36.1, 30.1, 28.4, 22.3, 20.1;

IR(film) 3377.1, 2966.1, 2871.1, 1714.0, 1513.3, 1455.9, 1366.0, 1250.0, 1174.1, 996.6, 938.7, 911.2 $cm^{-1}$;

Exact Mass Calc. for $C_{19}H_{33}NO_3$ $[M + Na]^+$ : 346.2353 ; found : 346.2353 (ESI)

**(*R*)-4-methyl-5-methylene-6-((*S*)-4-methylhex-5-en-1-yl)-2,3,4,5-tetrahydropyridin-1-ium 2,2,2-trifluoroacetate (S3)**



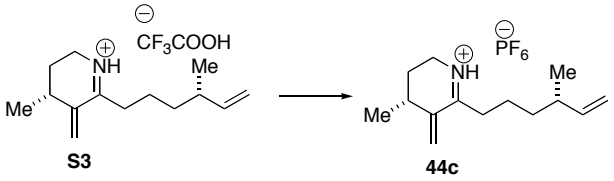

Amide **S2** (320 mg, 0.989 mmol, 1 eq) was dissolved in 2 mL $CH_2Cl_2$ and 2 mL TFA was added dropwise. Bubbling ensued. After 5 minutes, volatiles were removed *in vacuo* to give a brown oil, which was dissolved in 10 mL $CHCl_3$ and refluxed for 2 hours. Volatiles were removed *in vacuo* to give a brown oil, which has the following partial characterization data, and was used without further purification.

$^1$H NMR (600 MHz, $CDCl_3$) δ 13.68- 13.45 (broad bump, 1H), 6.38 (s, 1H), 6.15 (s, 1H), 5.60 (ddd, $J$ = 14.3, 9.8, 8.3 Hz, 1H), 4.98- 4.93 (m, 2H), 3.91- 3.83 (m, 1H), 3.83- 3.76 (m, 1H), 2.90- 2.82 (m, 2H), 2.73- 2.65 (m, 1H), 2.16- 2.05 (m, 2H), 1.77- 1.69 (m, 1H), 1.69- 1.56 (m, 2H), 1.43- 1.31 (m, 2H), 1.27 (d, $J$ = 6.9 Hz, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 180.4, 160.6 (multiplet), 143.3, 140.0, 132.4, 113.6, 43.5, 37.4, 35.8, 33.3, 30.5, 27.1, 26.8, 20.1, 18.6;

$^{19}$F NMR (470 MHz, $CDCl_3$) δ -76.4 ppm

**(*R*)-4-methyl-5-methylene-6-((*S*)-4-methylhex-5-en-1-yl)-2,3,4,5-tetrahydropyridin-1-ium hexafluorophosphate(V) (44c)**




The brown oil from the preceding step was dissolved in 10 mL $CH_2Cl_2$ and washed vigorously twice with 5 mL saturated $NaPF_{6(aq)}$. The organic layer was dried over $Na_2SO_4$. Solvent was removed *in vacuo* to give **44c** as a greasy brown solid (344 mg, 0.981 mmol, 99 % yield) in sufficient purity to be used without further purification.

Characterization data:

$[\alpha]^{20}_D$ = +28.9 (*c* 2.89, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 10.84- 10.38 (broad bump, 1H), 6.41 (s, 1H), 6.20 (s, 1H), 5.63 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 4.99 (ap. d, *J* = 17.1 Hz, 1H), 4.95 (ap. d, *J* = 10.3 Hz, 1H), 3.97- 3.83 (m, 2H), 2.93- 2.81 (m, 2H), 2.74- 2.69 (m, 1H), 2.17- 2.07 (m, 2H), 1.80 – 1.72 (m, 1H), 1.72- 1.62 (m, 2H), 1.48- 1.35 (m, 2H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H);

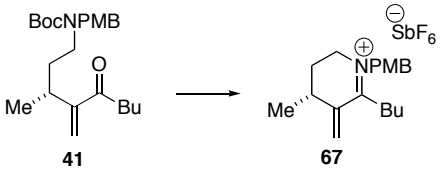
$^{13}$C NMR (125 MHz, $CDCl_3$) δ 181.4, 143.5, 140.0, 132.8, 113.6, 44.3, 37.4, 35.9, 34.2, 30.4, 27.2, 26.3, 20.2, 18.6;

$^{19}$F NMR (470 MHz, $CDCl_3$) δ -72.6 (d, $^1J_{PF}$ = 713 Hz);

IR(film): 3649.3, 3329.1, 2965.1, 1654.2, 1458.0, 1418.9, 1334.2, 1202.4, 841.3 $cm^{-1}$

Exact Mass Calc. for $C_{14}H_{24}N$ [M cation]$^+$ : 206.1903 ; found : 206.1874 (ESI)

**(*R*)-6-butyl-1-(4-methoxybenzyl)-4-methyl-5-methylene-2,3,4,5-tetrahydropyridin-1-ium hexafluoroantimonate(V) (67)**




Enone **41** (456 mg, 1.13 mmol, 1 eq) was dissolved in 3 mL $CH_2Cl_2$ and 3 mL trifluoroacetic acid was added. After 5 minutes the volatiles were removed *in vacuo* and the residue was redissolved in 5 mL $CHCl_3$. Five drops of TFA were added and the mixture was refluxed for 14 hours. The solvent was removed *in vacuo* and $^1$H NMR analysis showed complete cyclization. The residue was dissolved in 6 mL of a 1:1 mixture of MeOH and $CH_2Cl_2$ and $HSbF_6$-$6H_2O$ (427 mg, 1.24 mmol, 1.1 eq) was added as a solid. The volatiles were removed *in vacuo* and the residue was azeotroped 3x 5 mL $CH_2Cl_2$. The residue was purified by flash chromatography (5% MeOH/ $CH_2Cl_2$) to yield 580 mg of iminium **67** (1.11 mmol, 97%) as a brown oil setting to a brown crystalline solid slightly below room temperature.

$R_f$ = 0.30 (10% MeOH in $CH_2Cl_2$, strongly UV active, stains yellow/white in CAM)

$[\alpha]^{20}_D$ = +9.1 (*c* 3.11, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 6.22 (s, 1H), 5.14 (d, *J* = 5.2 Hz, 1H), 5.05 (s, *J* = 5.2 Hz, 1H), 3.89- 3.78 (m, 2H), 3.83 (s, 3H), 3.10- 3.03 (m, 1H), 3.02- 2.96 (m, 1H), 2.77- 2.70 (m, 1H), 2.77- 2.70 (m, 1H), 2.12- 2.07 (m, 1H), 1.74- 1.67 (m, 1H), 1.49 (pent. *J* =7.3 Hz, 2H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 181.2, 160.5, 141.4, 133.2, 129.1, 122.3, 115.1, 59.6, 55.4, 52.2, 31.2, 30.4 (2 signals), 27.8, 22.9, 18.9, 13.3;

IR(film) 2964.9, 1610.4, 1515.6, 1463.7, 1254.0, 1181.3, 1029.6, 832.8, 657.6 $cm^{-1}$;

Exact Mass Calc. for $C_{19}H_{28}NO^+$ $[M]^+$ : 286.2165 ; found : 286.2153 (ESI)

# *Chapter 6*

## Diels Alder Studies: Olefin Isomerization

### I. Reevaluation of the Stereochemistry of the Pero Model

The studies in the previous chapters culminated in the synthesis of elaborate *Z*-diene **1** , model *Z*-diene **2**, elaborate iminium **3** and model iminium **4** (Figure 6.1). This chapter will describe the studies of their respective Diels–Alder reactions.

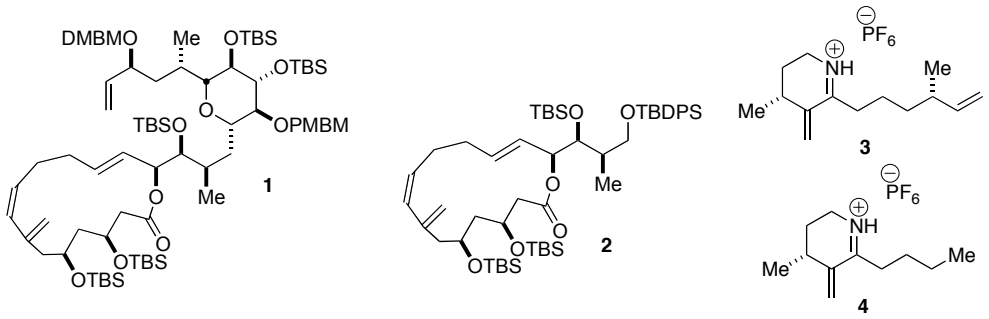
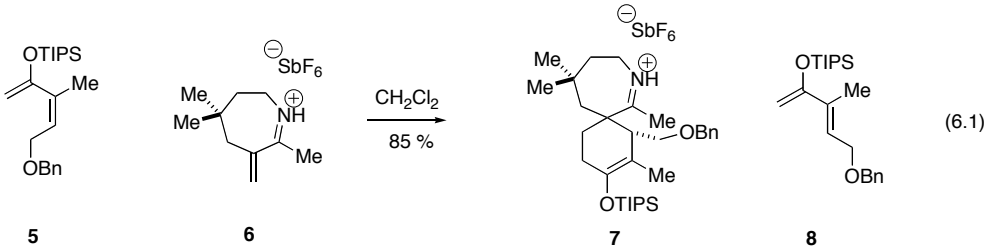



**Figure 6.1** Dienes and Dienophiles

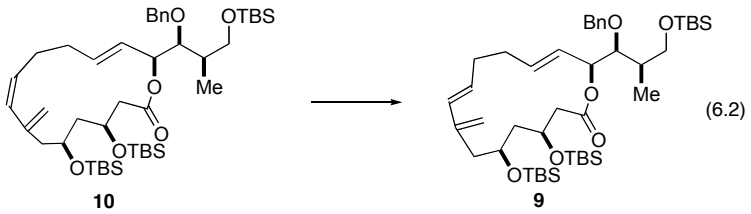
After the development of the viable Diels–Alder reaction with protonated iminium ions, this strategy was extended by Dr. David Marcoux in the course of the synthesis of the spirolide spiroiminium core. Dr. Marcoux had attempted some Diels–Alder reactions between acyclic *Z*-enolsilane containing diene **5** and iminium **6**, and in addition to product **7**, he recovered some isomerized diene **8**. (Equation 6.1)




Dr. Pero had also been aware of diene isomerization in the course of some of his unsuccessful intramolecular Diels–Alder reactions (Chapter 3 Section III). I had assumed

that no isomerization was occurring in my Diels–Alder reactions, based on the spectral similarity of my results with Dr. Pero's. A further piece of data that reassured me was that *Z*-diene **1** and **2** could be observed throughout the Diels–Alder reactions I conducted under optimized conditions, and could be recovered intact from reactions that were not run to completion. However, this does not preclude a scenario where the *E*-diene is consumed as soon as it is formed and cannot build up in a detectable concentration. Dr. Pero had noted that *E*-diene **9** was consumed at a much faster rate than *Z*-diene **10**.[1]

Out of an abundance of caution, it was decided to devise an experiment to test if this scenario was operative. It was noted that samples of *Z*-diene **10** prepared by Borg and Pero that were anywhere from 3 to 5 years old, and had been stored continuously at -20 °C, contained various amounts of *E*-diene **9** (anywhere from 10 to 30 %) (Equation 6.2). This *E* diene **9** directly corresponded with authentic samples prepared from the ene-yne metathesis route shown in Chapter 3.

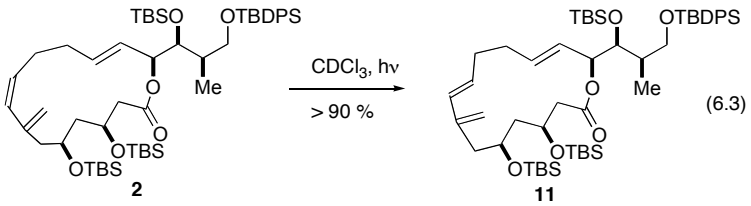



(6.2)

I did not want to revisit the ene-yne metathesis route at this point, as the material that Dr. Bindschädler had prepared was beyond the point at which the ene-yne metathesis route diverged. Based on the hypothesis that the isomerization was mediated by Brønstead acids, a sample of macrocycle **2** was dissolved in chloroform-d and taped in a window,

(1) Such scenarios have been reported or postulated in the literature: see (a) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 6282- 6284. (b) Franzini, M.; Zanoni, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 4837- 4841.

exposed to sunlight. Clean isomerization to *E*-diene **11** was complete within 48 hours (Equation 6.3).[2]



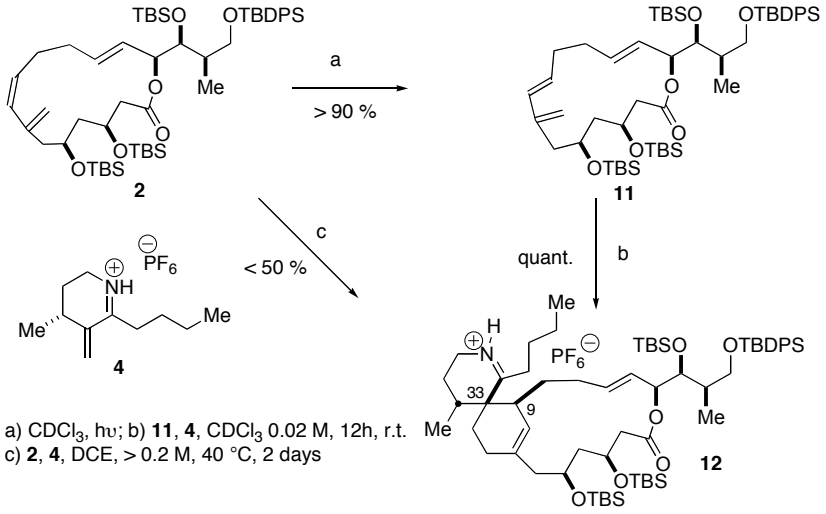

(6.3)

Verification that it was not light but photogenerated acid mediating the transformation employed the following experiment: three NMR tubes were filled with chloroform-d, 2 tubes of which contained model macrocycle **2**. One tube contained just chloroform. One tube containing model macrocycle **2** was wrapped in aluminum foil, and the other tubes containing model macrocycle **2** and the tube containing just chloroform were taped in the window. When isomerization of **2** to **11** in the tube exposed to light was complete, an NMR spectrum was taken of the sample kept in the dark, and no isomerization was detected. The chloroform in this sample was removed, and replaced with the chloroform from the blank tube that had been exposed to light. The tube was returned to the dark for 2 days, and after that time an NMR experiment showed complete isomerization of **2** to **11**.

The *E*-diene **11**, obtained by the acid mediated isomerization was subject to a Diels–Alder reaction with model iminium **4**, and unfortunately the product **12** obtained was identical to the product that was obtained from the Diels–Alder reaction of the *Z*-diene under the conditions used in Chapter 5 (Scheme 6.1). The stereochemical assignment will be explained shortly, as it also does not follow from the stereochemical model originally proposed.

(2) Identification of this compound was based on *J* couplings of the olefins in the $^{1}$H NMR spectrum, and similarity of the spectrum to macrocyclic *Z*-dienes prepared by Dr. Borg.

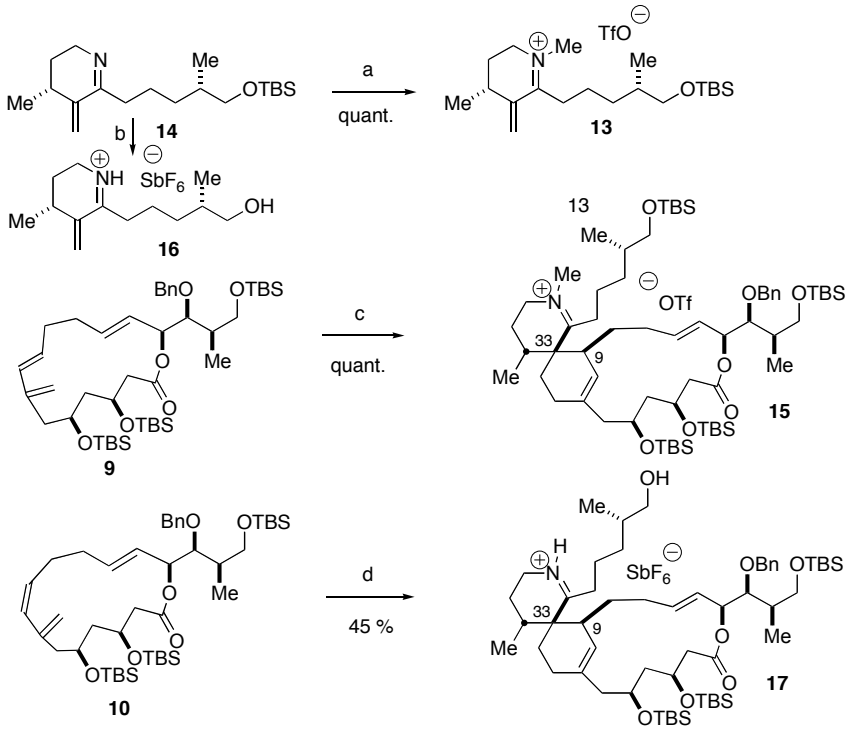
**Scheme 6.1**




This result means that the Diels–Alder reactions described in the preceeding chapter had not generated the correct stereochemistry at $C_{33}$. Unfortunately, this also means that the results reported by Pero also provided the incorrect $C_{33}$ to $C_9$ stereochemical relationship. The reason Pero did not catch this was because in his studies he had allowed *E*-diene **9** to react with only the methylated iminium **13** derived from imine **14**, to give product **15**. *Z*-diene **10** was allowed to react only with the protonated iminium **16** derived from imine **14** to give product **17** (Scheme 6.2). This precluded direct comparison of the NMR spectra as **15** and **17** had different iminium structures. In retrospect, the $^1$H spectra of **15** and **17** are similar enough that it is almost certain the two products had the same $C_9$–$C_{33}$ configurations.[3]

(3) Dr. Pero's archival samples of **15** and **17** had decomposed after 4.5 years of storage before I reached this realization. Inspection of the 2D ROESY spectra that he left almost certainly support my assignment, though because of the small quantity of **16** that Dr. Pero obtained, that ROESY spectrum in particular contained a lot of ambigious noise. In section II of this chapter, I prepare compounds of the correct $C_9$-$C_{33}$ configuration that have markedly different $^1$H NMR spectra.

**Scheme 6.2**[4]




a) **14**, MeOTf, $CH_2Cl_2$; b) **14**, $AgSbF_6$, BnBr, $CH_2Cl_2$ c) **13**, $CH_3CN$, 0 °C; d) **16**, DCE, 40 °C

With ample quantities of Diels–Alder adduct **12** in hand, ROESY spectroscopy was employed to determine the stereochemistry around the spiro-centre and iminium.[5] Upon irradiation of the proton at $C_9$ , a strong signal corresponding to the methyl group at $C_{34}$ was observed. This is consistent with the stereochemistry shown in Figure 6.2.

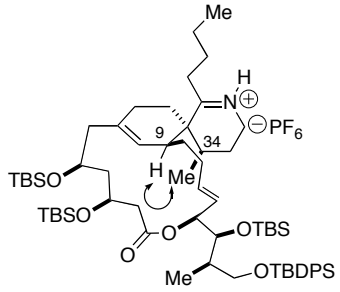


**Figure 6.2** Stereochemistry of Diels–Alder adduct **12**.

(4) The experiments in this scheme were performed by Dr. Joseph Pero, I made the stereochemical assignments indicated.

(5) nOe spectroscopy is ineffective with these Diels–Alder adducts, extended irradiation results in little to no correlation. The molecular weight/shape must be in a regieme where rates of molecular tumbling are not averaged out in the timeframe of the NOESY pulse sequence. For a review on selecting the best NMR experiments for molecular size, see: Reynolds, W. F.; Enríquez, R. G. *J. Nat. Prod.* **2002**, *65*, 221-244.

This means that product **12** must have arisen from an endo attack of the diene syn to the methyl group on iminium **4**. Such an orientation in the transition state is represented by structure **18** in Figure 6.3. Up until that point, we had expected that the attack of the macrocyclic diene would occur anti to the methyl group on the iminium, represented by structure **19**, which would lead to product **20**. Product **20** would have the correct configuration at $C_{33}$, but the incorrect configuration at $C_9$. In fact, with acyclic *E*-dienes, attack anti to the methyl group had been observed,[6] and until the ROESY study we believed that products **12** and **15** actually had the configurations at $C_{33}$ and $C_9$ depicted in hypothetical product **20**.

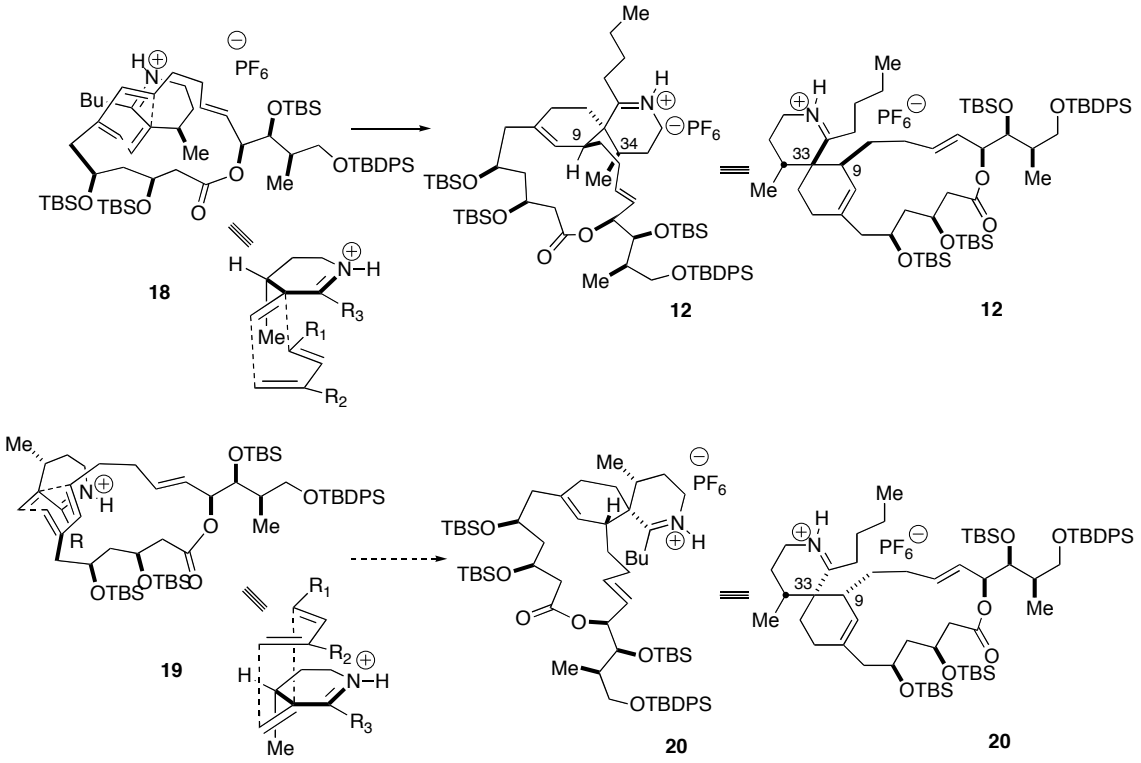



**Figure 6.3** Endo orientations of cycloadditions on *E*- dienes.

This stereochemical outcome suggested that the macrocycle itself had a facial bias. In Figure 6.4, hypothetical transition state **21** shows how an attack anti to the methyl group on **4** by the favoured face would necessarily go through an exo transition state, leading to

(6) Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G.; Evans, D. A. *Org. Lett.* **2011**, *13*, 3758- 3761.

product **22**, which would possess the desired stereochemistry. A final possibility would be an exo reaction of the disfavoured face, syn to the methyl group on **4**, depicted in transition state **23** which would give product **24**, possessing incorrect stereochemistry at both $C_9$ and $C_{33}$. This path was judged very unlikely, as the back of the diene would clash with the methyl at $C_{34}$ in the transition state, and there would be a syn-pentane interaction between $C_{10}$ and the $C_{34}$ methyl in product **24**.

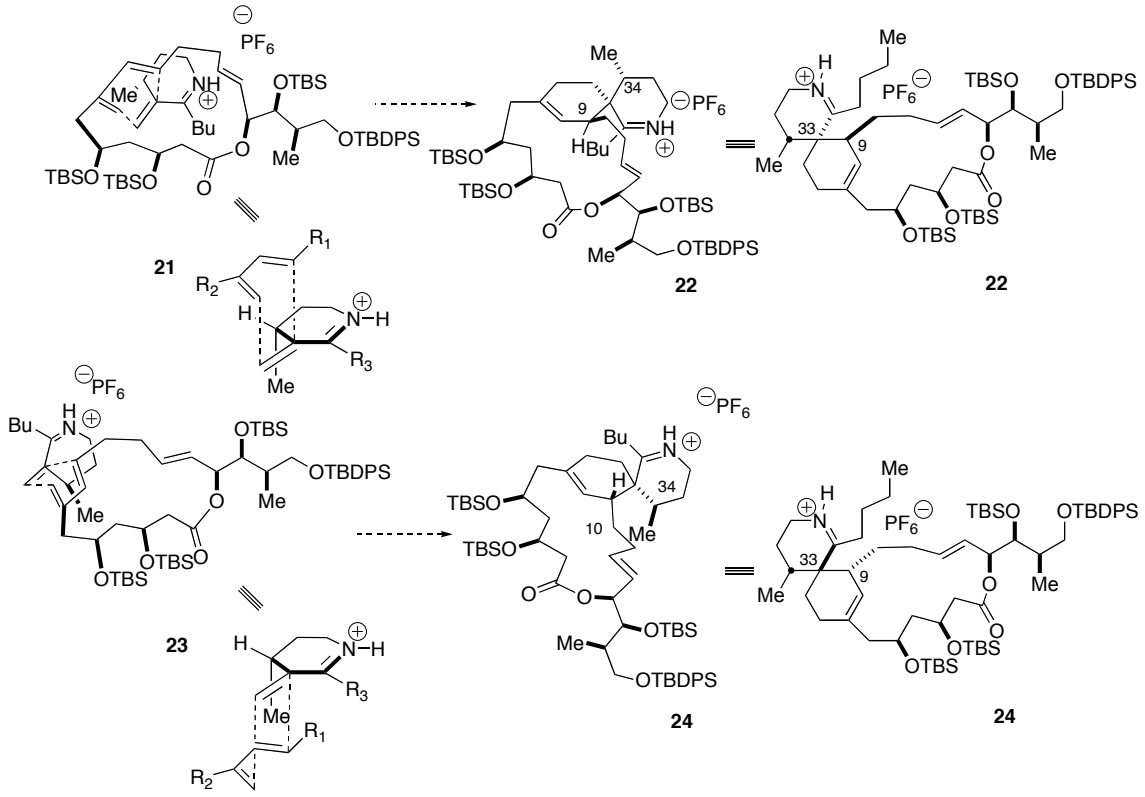


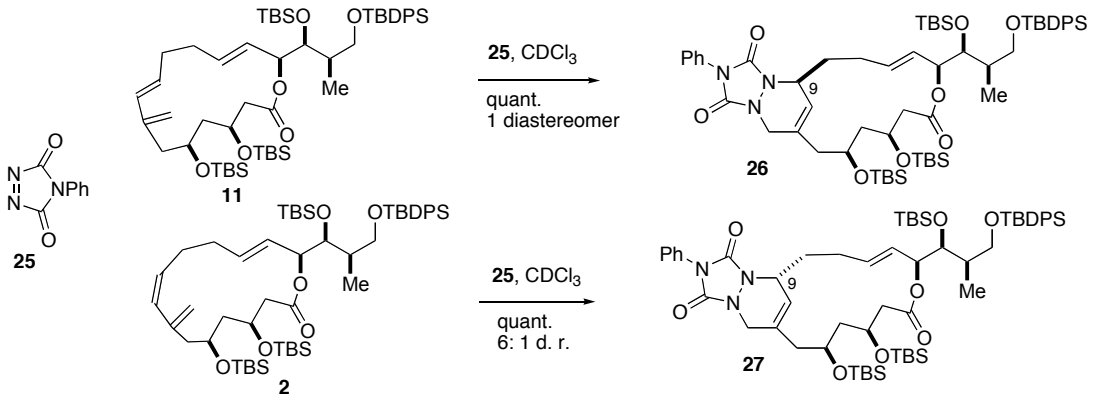

**Figure 6.4** Unlikley exo orientations of cycloadditions.

With the new hypothesis that the *E*-macrocyclic diene has a pronounced facial bias, studies were undertaken with the reactive dienophile PTAD **25** to attempt to confirm this. PTAD is a reactive dienophile, that reacts via *endo* transition states and has been used before to assess facially biased dienes,[7] and simplifies the analysis since both an exo and

(7) For use of PTAD to assess facial bias, see: a) Marchand, A. P.; Ganguly, B.; Shukla, R. *Tetrahedron*, **1998**, *30,* 4477-4484. b) Morrison, C. F.; Vaters, J. P.; Miller, D. O.; Burnell, D. J. *Org. Biomol. Chem.*, **2006**, *4*, 1160-1165. It should be noted that PTAD does undergo non-concerted reactions with very electron rich dienes, but a concerted reaction was assumed for the cases shown above. See: Clennan, E. L.; Earlywine, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 7104- 7110. A computational study by Houk suggests that

endo transition state would give the same product (Scheme 6.3). In the event, *E*-diene **11** was mixed with **25**, and at room temperature the reaction appeared to be essentially instantaneous as judged by the loss of the red colour of the PTAD. PTAD adduct **26** was obtained as a single product. The $^1$H NMR spectrum of PTAD adduct **26** bore close resemblance to that of **12**, with chemical shifts of the protons at $C_8$ , $C_{12}$, $C_{13}$ and $C_{14}$ being almost superimposable. On this basis, the structure of **26** was assigned as being homologous to **12** at $C_9$.[8] This result supports the idea that the *E*- macrocyclic diene has a strong facial bias. When coupled with the strong bias of **4** to react via an endo transition state, Diels–Alder adduct **12** is obtained.[9]

**Scheme 6.3**




The analogous reaction with *Z*-diene **2** also proceeded essentially instantaneously, with decolorization of the PTAD stock solution occurring immediately upon mixing with a solution of **2**. In this case, two diastereomers were obtained in approximately a 6:1 ratio, with the minor adduct being **26**. The $^1$H NMR spectrum of the major adduct, **27**, was very different to that of both iminium adduct **12** and PTAD adduct **26**, supporting the earlier

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concerted reactions via an endo transition state are favoured on non-oxygen substituted dienes with PTAD: Chen, J. S.; Houk, K. N.; Foote, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 12303- 12309. The endo transition state arises since there would be a repulsion between the nitrogen lone pairs and the π system in the exo transition state.

(8) Unfortunately compound **26** was not solid, and attempts to remove TBS groups led to decomposition, precluding analysis by X-Ray diffraction.

(9) For the analogous use of N-phenyl maleimide to probe the *endo*/*exo* selectivity of a macrocyclic diene, see: Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12036- 12041.

assignment of **26** by anaology. $^{1}H$ and $^{13}C$ analysis of **27** showed it did not arise from modes of reaction other than a 4+2, such as an ene reaction.

These studies suggest that the reaction of *Z*-diene **2** with iminium **4** to give **12** must be occurring through an isomerization. For **12** to arise from a Diels–Alder reaction of **4** and **2** without isomerization of **2** would involve an exo attack of the minor conformer of the *Z*-diene syn to the methyl group, shown in transition state **28**, Figure 6.4. Such an attack would be imagined to have a steric clash between $C_8$ on the back of the diene and the methyl at $C_{34}$. The other reaction syn to the methyl group via an endo mode, shown in **29** would give syn pentane interaction containing product **24** and is also judged unlikely.

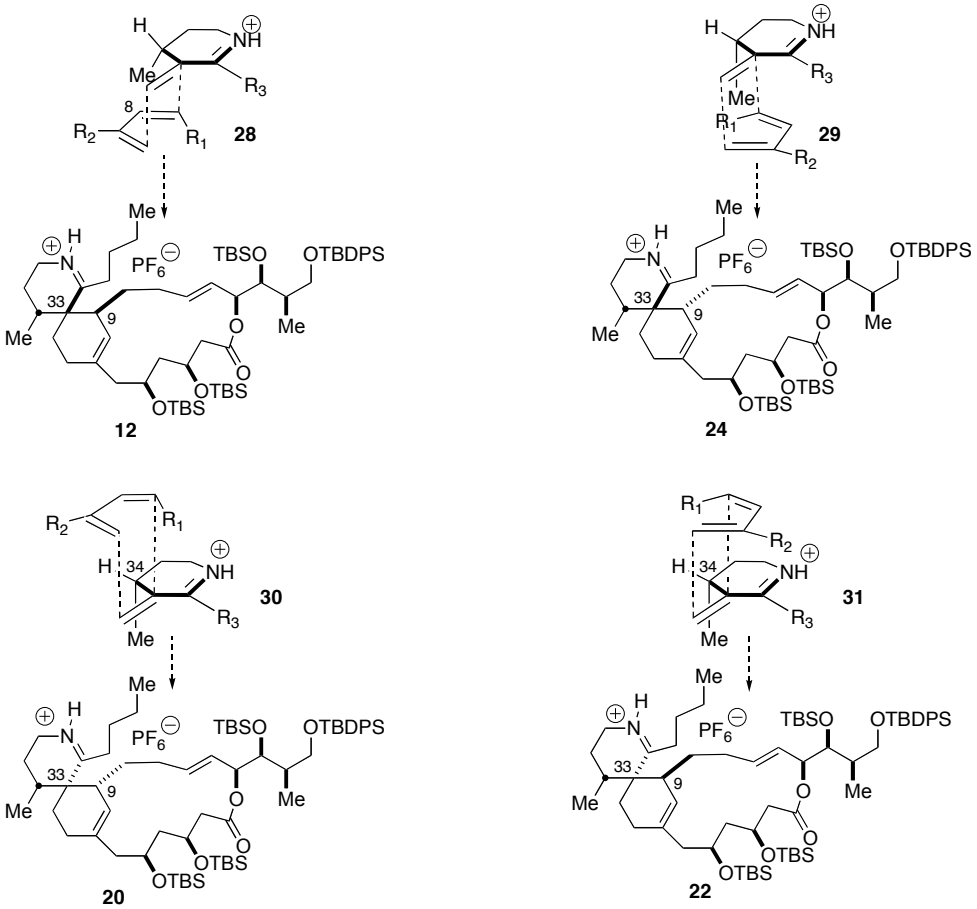


**Figure 6.5** Modes of reaction of macrocyclic *Z*-dienes.

There are two modes of addition that may occur anti to the methyl group. A exo mode anti to the methyl group, shown in transition state **30**, would give compound **20**. This cycloaddition would go through what the PTAD results suggest is the major conformation of the diene, however, the exo transition state may be undesirable as the $C_7$-$C_8$ bond at the back of the diene is placed over the $sp^3$ centre at $C_{34}$. Transition state **31** shows the desired orientation of the reactants that would lead to compound **22**, bearing the desired $C_{34}$–$C_{33}$–$C_9$ stereochemical relationship. While this goes through an endo transition state, it would also be on the minor conformer of the *Z* diene, and it is unclear if the steric interaction between $C_{10}$ on the diene (represented as $R_1$) and the $sp^3$ centre at $C_{34}$ would disfavour this transition state more than transition state **30**.

To summarize the above observations, it may be said that the *Z* and *E* macrocyclic olefins are probably in similar conformations and present the same face of the diene (*ie* the *Re* face of the olefin at $C_7$. What makes the *E* diene present the correct face and the *Z* diene present the incorrect face with respect to the desired product is the change in configuration at $C_9$. This stylized in structures **32** and **33**, shown in Figure 6.6.

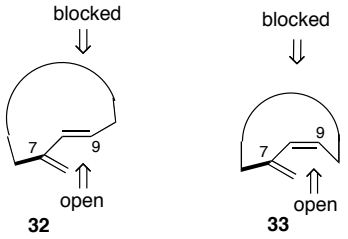


**Figure 6.6** The same diene face is presented in each macrocycle.

It may be anticipated from the results described above that forming the correct stereochemistry at $C_{33}$ and $C_9$, shown in product **22** will be difficult. *E*-diene **11** must react through exo transition state **18**, which is disfavoured by dienophile **4**, while to access the correct stereochemistry with *Z* diene **2**, it must react through the minor

conformer in endo transition state **31** which possesses a steric interaction between $C_{10}$ and $C_{34}$.

## II. Attempts to Promote an Exo Transition State

Faced with the setback that the correct stereochemistry had not yet been accessed in the Diels–Alder reaction, we were faced with three possible solutions:

The first, or least motion principle was to find some method of suppressing the isomerization of *Z*-dienes. The second option would be to find some way to force an exo transition state on the more reactive *E*-diene. The third option would be to abandon the iminium Diels–Alder reaction and further investigate the elaboration of the lactam Diels–Alder adducts prepared by Brandl and Chiu (Chapter 3). Efforts initially focused on the second option, since the *E* diene did present the correct face and was more reactive than the *Z* diene. There is no general method to overturn endo/exo selectivity, so this appeared to be an attractive research area.

To briefly summarize, three different routes to modify dienophile **4** to become exo selective were attempted. Mono or bis halogenation α to the iminium was considered. It was postulated steric bulk at this position would disfavour endo transition states **34** and **35**. Unfortunately a number of efforts to halogenate **4** failed.[10] To test the principle, *tert* butyl iminium **36** and isopropyl iminium **37** were prepared. These systems were not reactive in Diels–Alder reactions with simple dienes, so this approach was abandoned (Figure 6.7).

(10) Conditions attempted on both iminium **4**, freebase **38** and PMB iminium included treatment with NCS, NBS, $I_2$, $CuBr_2$ and Barluenga reagent ($[SymCollidine_2I]^+PF_6^-$). Iminium salts were generally unreactive with these reagents, while the freebase was decomposed.

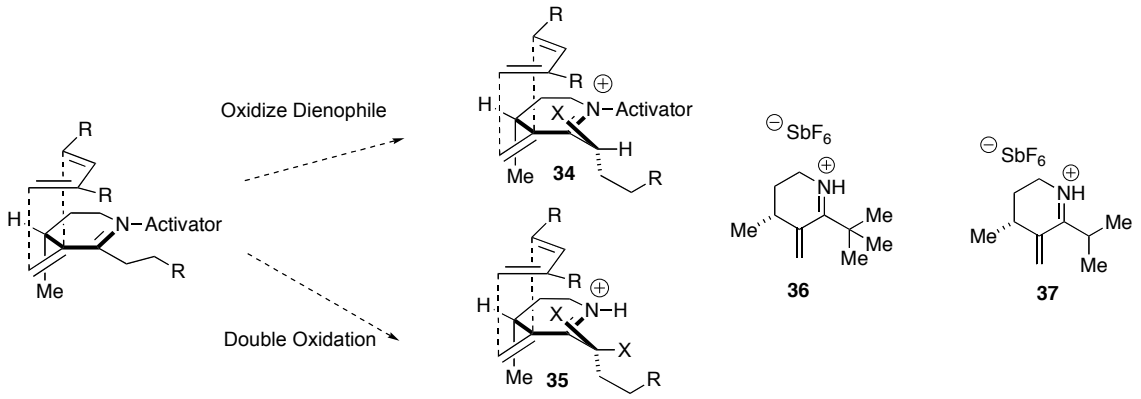


**Figure 6.7** Attempts to force an exo transition state with α substituents.

Another attempt was made to use bulky Lewis acids to activate the nitrogen, shown in Figure 6.8. Imine **38** could be prepared from iminium **4** by a simple aqueous sodium hydroxide wash.[11] The yield for this deprotonation was high, but could not be measured precisely because of the marked volatility of **38**. Imine **38** was notably unstable, and was typically used immediately after preparation. Compound **38** could be complexed with various Lewis acids to form the corresponding adducts. Gold complex **39** was prepared, but was not reactive, even with isoprene.[12] Complex **39** was markedly more stable than parent imine **38**. Mixing **38** with tris-pentafluorophenylborane led to complex **40**, as ascertained by desymmetrization in the $^{19}F$ NMR spectrum. This complex was not stable, and decomposed on a time scale incompatible with a Diels–Alder reaction.[13] Attempts to form complex **41**, with trityl BArfate salts led to decomposition of **38**.[14]

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(11) Dr. David Marcoux originally showed that iminium **6** was stable to these conditions. Our previous method of forming **38** was chromatography of **4** with 1% $Et_3N$ in $CH_2Cl_2$, which provides inferior yields and product quality.

(12) The AuCl carbene complex was treated with $AgSbF_6$, then **38**. See: de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics*, **2005**, *24*, 2411- 2418.

(13) Bergquist, C.; Bridgewater, B. M.; Harlan, J. C.; Norton, J. R.; Friesner, R. A.; Parkin, G. *J. Am. Chem. Soc.* **2000**, *122*, 10581- 10590.

(14) New peaks on the olefin region of the $^1H$ NMR spectrum were observed, and it is suspected oxidation of **38** by hydride abstraction occurred. For trityl borate oxidations, see: Straus, D. A.; Zhang, C.; Tilley, T. D. *J. Orgmet. Chem.* **1989**, *369*, C13- C17.

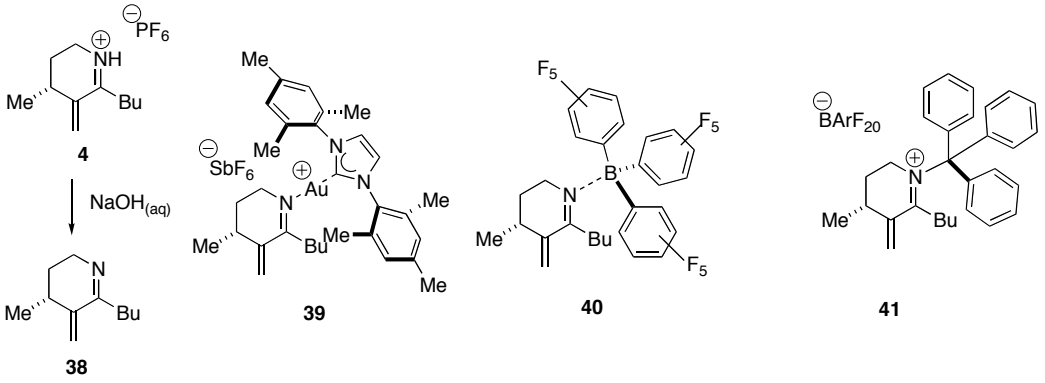



**Figure 6.8** Attempts to employ bulky Lewis pair adducts.

A final concept was employed, the use of electron rich tetraarylborate complexes. These are known to associate with NH cations as shown in structure **42**, and it was hoped that tetraarylborates with meta substituents may shield areas in which substituents on the diene would need to sit in an endo transition state, therefore favouring exo transition state **43**.[15]

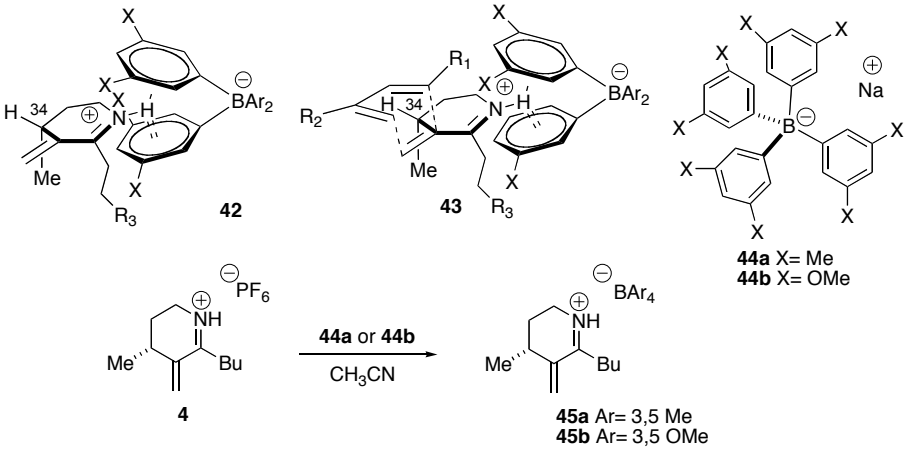



**Figure 6.9** Attempts to peturb diastereoselectivity with bulky borates.

Sodium tetraarylborates **44a** and **44b** with 3,5 methyl and methoxy substituents were prepared,[16] and it was found that mixing these compounds with the hexafluorophosphates

(15) Hydrogen bonds in ammonium tetraphenylborate to the midpoints of the aryl rings have been characterized by neutron diffraction. See: Steiner, T.; Mason, S. A. *Acta Cryst.* **2000**, B56, 254- 260.

(16) For the preparation of the sodium tetraarylborate salts, originally used as aryl sources in rhodium mediated aryl conjugate additions, see: Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.*, **2009**, *131*, 13588- 13589.

in acetonitrile resulted in the precipitation of sodium hexafluorophosphate to produce iminiums **45a** and **45b**. NMR spectra of these iminium ions in chloroform revealed an association as evidenced by large perturbations in the chemical shifts of various protons on the iminium ion, while the same compounds desolved in acetonitrile had spectra that were almost superimposable with the hexafluorophosphate salts, indicating a lack of association. It was also striking that the acetonitrile solutions were colourless, while solutions in chloroform were bright yellow.[17] This colour change was reversible upon removal and exchange of solvents, as were the changes observed in the NMR spectra. It was also observed that the solutions in chloroform were light sensitive, rapidly changing to an orange colour under exposure to sunlight. Unfortunately even when protected from the light, solutions of the iminium borates in halogenated solvents were not sufficiently stable to enable Diels–Alder reactions to be conducted.[18]

**III. Solution to the Isomerization of the Diene**

With the difficulty encountered in forcing the Diels–Alder reaction to undergo an exo transition state on an E diene, it was decided to pursue the first option, that of suppressing the isomerization. While no decomposition of the dienophiles had been observed by $^1$H NMR, it is entirely possible that a quantity of acid arising from decomposition below the $^1$H NMR detection limits would still be sufficient to conduct isomerization under the reaction conditions. It was also possible the solvent itself was decomposing to something acidic under the reaction conditions. Modulating the solvent proved to be ineffective. The dienophile is not soluble in less polar solvents, while the diene is not soluble in more polar solvents. Mixtures of solvents were difficult to employ as volatility differences

(17) Coloured complexes have been observed with N-acylammonium tetrafluoroborates: King, J. A. Jr.; Bryant, G. L. Jr. *J. Org. Chem.*, **1992**, *57*, 5136- 5139.

(18) Hypothesis for the lack of stability are the potential protonation of aryl ligands on the electron rich borates, or alternately a Fridel–Crafts reaction between the iminium and the electron rich aryl borate. The acetonitrile solutions appear indefinitely stable, so some aspect of the tight association in halogenated solvents drives the decomposition.

coupled with evaporation into the headspace of the flask often resulted in sufficient changes in composition to promote oiling out of one component. Trifluorotoluene was explored as a solvent, but any improvement over dichloroethane was marginal.[19] The addition of some kind of acid scavenger to the Diels–Alder reaction was attempted. Since the proton is required for the Diels–Alder reaction, it was initially thought that this could not be a stoichiometric base. Accordingly some experiments were carried out where solutions of Stang's base **46**, proton sponge **47** or pyridine **48** were titrated into three separate lots of iminium ion **4** in an NMR tube. Strikingly different results were obtained. Addition of Stang's base or proton sponge resulted in the precipitation of a solid, and the gradual upfield migration of the exo iminium peaks until at the addition of one equivalent of the base the spectum was that of the free base imine **38**.[20] In the pyridine experiment, as one eqivalent of pyridine was titrated in in steps of 10%, the iminium peak broadened and finally disappeared, but the exomethylene peaks remained unpeturbed. Even if substoichiometric amounts of **46** and **47** were used, decomposition of the iminium ion in its entirety was observed over 24 hours.

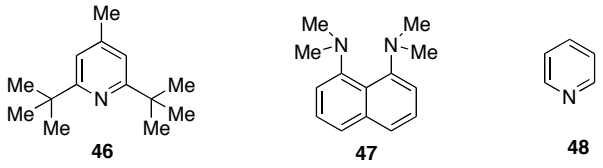



**Figure 6.10** Bases employed in NMR titration.

Based on the above results, it was judged that pyridine would have least peturbation on the reaction, so a Diels–Alder reaction with **2** was prepared with 2 equivalents of dienophile **4** and one equivalent of pyridine. After heating to 40 °C for 18 hours, NMR studies showed that diene **2** was intact, but the dienophile had completely decomposed. This result can be understood as a consequence of the previously observed lack of

(19) Curran has championed the use of trifluorotoluene as an environmentally friendly replacement for $CH_2Cl_2$. Akiya, O.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450- 451.

(20) The bases are not present in the NMR spectrum as it appears the hexafluorophosphate salts of the conjugate acids are completely insoluble in $CDCl_3$.

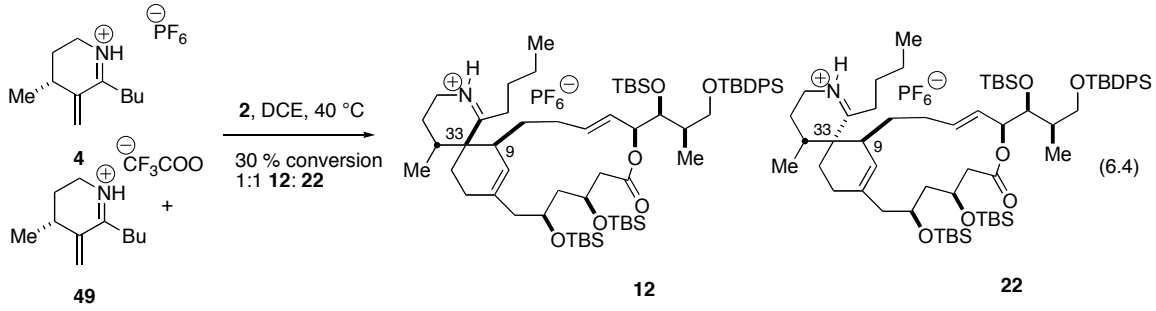
stability of the free base imine **38**. Presumably, the imine decomposes to products that are also basic, and so the proton can be transferred from intact iminium to decomposed imine, generating more imine to be decomposed. The overall outcome is that a catalytic amount of base results in complete decomposition of the iminium.

A possible solution was using a base whose conjugate acid has a pKa much less than that of the iminium, but is still insufficiently acidic to effect the isomerization of the diene. This would keep the iminium protonated throughout the Diels–Alder reaction. Trifluoroacetate is a potential candidate. It had already been documented by Dr. Borg that iminium trifluoroacetates do not engage in Diels–Alder reactions with the macrocyclic dienes, but also do not decompose them. This is actually the main reason hexafluorophosphate was used instead of hexafluoroantimonate as the non-coordinating counterion in the final synthesis of **4** described in Chapter 5.[21] This change allowed the ratio of hexafluorophosphate to trifluoroacetate to be observed by $^{19}F$ NMR throughout the reaction.

A preliminary experiment with a 2 equivalents of a 6: 1 ratio of hexafluorophosphate iminium **4** to trifluoroacetate iminium **49** was set up with the macrocyclic diene in DCE as the solvent. Gratifyingly, a new product diastereomer, tentatively assigned as **22**, was present in an approximately 1:1 ratio with the undesired diastereomer. Unfortunately this mixture of **12** and **22** was not seperable, so at the time pure **22** for NMR studies could not be obtained. This finding bolstered the idea that buffering the reaction mixture could improve diastereoselectivity (Equation 6.4). The mixture of **4** and **49** could be held for several days under vacuum and the ratio of hexafluorophosphate to trifluoroacetate

(21) Phosphorous is S=1/2 and hexafluorophosphate is well behaved in $^{19}F$ NMR specta (Antimony consists of two naturally abundant isotopes, $^{121}Sb$ is spin 5/2 and $^{123}Sb$ is spin 7/2. Hexafluoroantimonate gives a very broad $^{19}F$ NMR signal and often can not be observed at all.)

remained constant. Interstingly, when the Diels–Alder reaction mixture was pumped down, with no other manipulation, the sample was enriched in hexafluorophosphate. It is unclear if this supports the idea the iminium is decomposing to something with a weaker conjugate base, as I also observed that the Diels–Alder adducts will slowly lose trifluoroacetic acid under vacuum.[22]




(6.4)

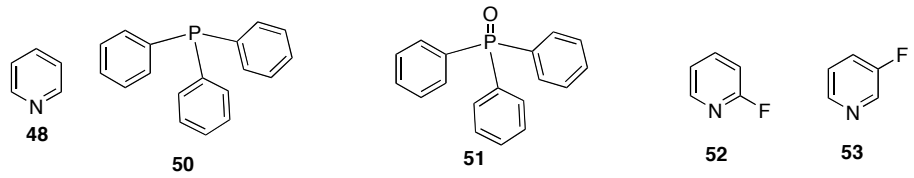
Unfortunately, attempts to increase the ratio of trifluoroacetate to hexafluorophosphate resulted in unacceptably slow reaction rates, which was not surprising given Dr. Borg's earlier results, and the importance of having non-coordinating counterions shown in Chapter 5.

It was decided to investigate neutral buffers that could be added to pure iminium hexafluorophosphate. Four possible candidates emerged, triphenylphosphine, triphenylphosphine oxide, 2-fluoropyridine and 3- fluoropyridine (Table 6.1).[23] Admixture of triphenylphosphine and iminium **4** resulted in immediate decomposition, but the 3 other bases generated mixtures that were completely stable for 24 hours at 40 ºC. It was decided that the volatile fluoropyridines were the best candidates for further investigation because of their ease of removal.

(22) A hypothesis for this observation is that the position of the equilibrium between protonated iminiums **12** and **22** and trifluoroacetic acid and free imine is sufficient to allow the trifluoroacetic acid to be pumped away over a several day time scale. It appears iminium **49** does not behave this way, but I did note that **49** does tend to bind excess trifluoroacetic acid, so it is possible that the time to remove this excess is longer. The accurate integration of trifluoroacetic acid in $^{1}$H spectra of **49** is difficult because the single proton is extremely broad.

(23) Triphenylphosphine pKa : Streuli, C. A. *Anal. Chem.,* **1960**, *32*, 985- 987. Fluoropyridine pKas : Brown, H. C.; McDaniel, D. H. *J. Am. Chem. Soc.* **1955**, *77*, 3752- 3755.

**Table 6.1** Screening of weak bases in the Diels–Alder reaction

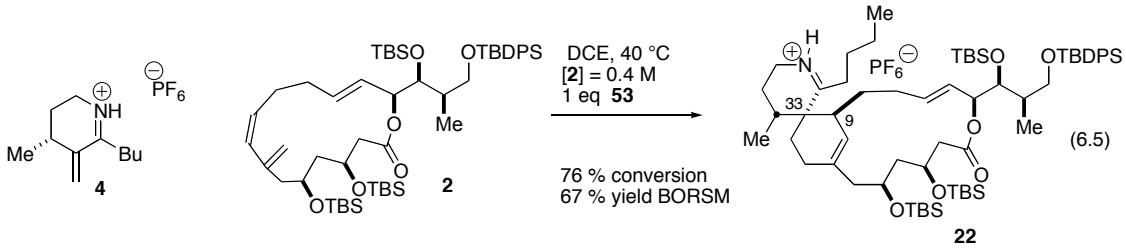



| entry | eq. Additive[a] | pKa of $BH^+$ | % conversion of **2**[b] | **12** : **22** |
|---|---|---|---|---|
| 1 | none | n/a | 50 | 3:1[c] |
| 2 | 0.5 eq. **48** | 5.25 | 0 | n/a[d] |
| 3 | 0.5 eq. **50** | 2.73 | 0 | n/a[d] |
| 4 | 1 eq. **52** | -0.44 | 30 | 1: 2 |
| 5 | 3 eq. **52** | -0.44 | < 10 | n/ d[e] |
| 6 | 1 eq. **53** | 2.97 | 50 | 1: 6 |
| 7 | 3 eq. **52** | 2.97 | < 10 | n/d[e] |

a) Relative to **2**. 3 eq of **4** were used relative to **2** b) After 48 hours reaction, 40 °C, [**2**]> 0.1 M in DCE c) On a 40 mg scale. On smaller scales the ratio of **2** to **22** is higher. d) **2** recovered unchanged, **4** decomposed e) Both **2** and **4** recovered unchanged

The base 3-fluoropyridine was judged to be the most promising, so was used in a preperative scale reaction with compounds **4** and **22** (equation 6.5). It is possible any 2-fluoropyridinium formed is still acidic enough to promote isomerization.

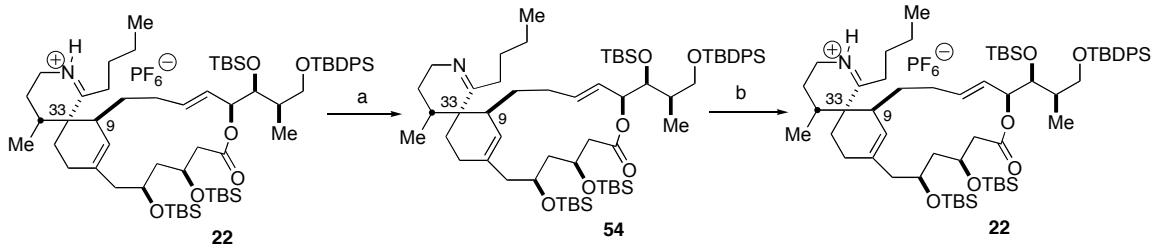
This reaction gave a 9:1 diastereoselectivity for product **22** in a preperative scale reaction (Equation 6.5). The reaction was allowed to go for 6 days, and reached 76 % conversion of **12** with a 52 % yield of **22** (67 % based on recovered starting material). Attempting to increase the temperature generally led to inferior results in the screening reactions.




With abundant supplies of **22** available, efforts were undertaken to assign the stereochemistry. First a pure sample of **22** needed to be obtained. This was best accomplished by deprotonation to form freebase **54**, followed by chromatography of **54**,

after which **54** was protonated with TFA and subject to counterion exchange to reform **22** (Scheme 6.4).[24]

**Scheme 6.4**




a) $NaOH_{(aq)}$, $CH_2Cl_2$; b) TFA, $CH_2Cl_2$; then $KPF_{6(aq)}$.

The 1D ROESY correlations are shown in Figure 6.11. ROESY correlations between the allylic proton at $C_9$ and the alpha protons at $C_{31}$ were observed in each direction in both $CDCl_3$ and $C_6D_6$.[25] This is taken as proof of the desired stereochemistry. The only other Diels–Alder adduct that could have these enhancements would be **24**, which would arise from an attack of the Z diene syn to the methyl group on **4** and would contain a syn pentane interaction. A ROESY correlation was also observed between the proton at $C_9$ and the proton at $C_{12}$.

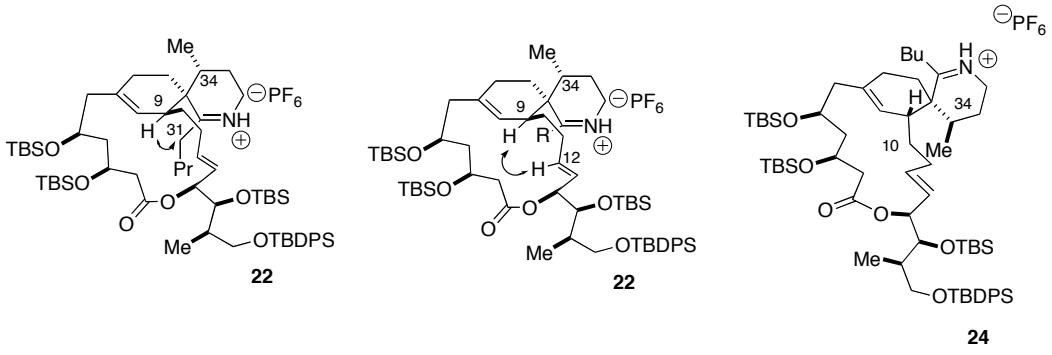



**Figure 6.11** ROESY correlations for the assignment of **22**.

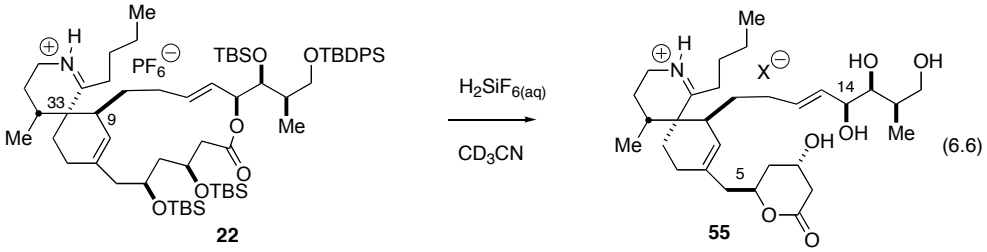
(24) Compounds **12** and **22** were not seperable by chromatography using MeOH/$CH_2Cl_2$ mixtures. Freebase **54** is seperable from the freebase of **12** by chromatography using EtOAc/hexanes, though the seperation is only feasible if the product ratio is high because the freebases streak even with $Et_3N$ additives. The streaking is attributed to tautomerization of the imine.

(25) The assignments of the protons that were irradiated were made by COSY and confirmed by TOCSY irradiations with low mixing times.

There was too much overlap in the aliphatic region to determine if there was a ROESY correlation between the proton at $C_{34}$ and the bridge at $C_{10}$.

### IV. Macrolactone Ring Contraction in Deprotection

Compound **22** could not be crystallized, so attempts to remove the protecting groups were undertaken. Exposure of **22** to hexafluorosilic acid resulted in complete removal of the silyl protecting groups.[26] Unortunately a large upfield peturbation was observed in the chemical shift of the proton at $C_{14}$. This suggested that the ester attachment had been lost. The mass spectrum suggested a lactone was still present, and $^1$H NMR studies suggested that structure **55** had formed (Equation 6.6).



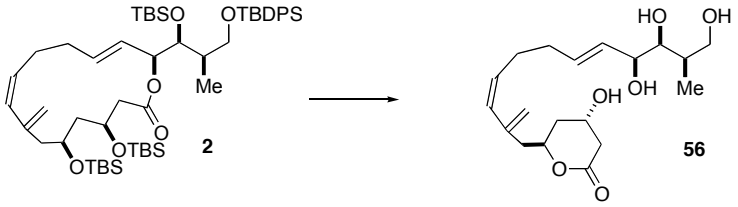

The analogous ring contraction also occurred with macrolactone **2** to give lactone **56**. A variety of conditions for the deprotection of macrolactone **2** were screened, and all appeared to promote this contraction (Table 6.2).[27] This is a problem that will need to be addressed for a successful completion of the synthesis. Given the poor results obtained with acetonide protection described in the next section, a reasonable possibility would be the use of TES groups in place of all of the TBS groups in the molecule. These should not peturb comformation too much, and milder conditions may enable deprotection without rearrangement. It is unclear if the TES groups could be introduced in the beginning or if a later stage protecting group swap would need to be made.

---

(26) a) for hexafluorosilicic acid see: Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58,* 5130- 5134. b) for TAS-F, see Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436- 6437.

(27) Aqueous hydrofluoric acid was potentially promising, and should be investigated further. The dominant product was **56**, but a small triplet was observed around 5 ppm, which may indicate unisomerized material.

**Table 6.2** Attempts to suppress macrolactone contraction on **2**.




| Entry | Reagent | Solvent | Outcome |
|---|---|---|---|
| 1 | CSA | MeOH/ $CH_2Cl_2$ | **56** |
| 2 | HF•py | THF | **56** |
| 3 | $H_2SiF_{6(aq)}$ | $CD_3CN$ | **56** |
| 4 | HF•py | THF/py | **56** |
| 5 | TAS-F | DMF-d7/ $D_2O$ | **56** |
| 6 | TBAF | THF | decomposition |
| 7 | TBAF | THF/AcOH | **56** |
| 8 | $Et_3N(HF)_3$ | $CD_3CN$ | **56**[a] |
| 9 | $HF_{(aq)}$ | $CH_3CN$ | **56**[a] |

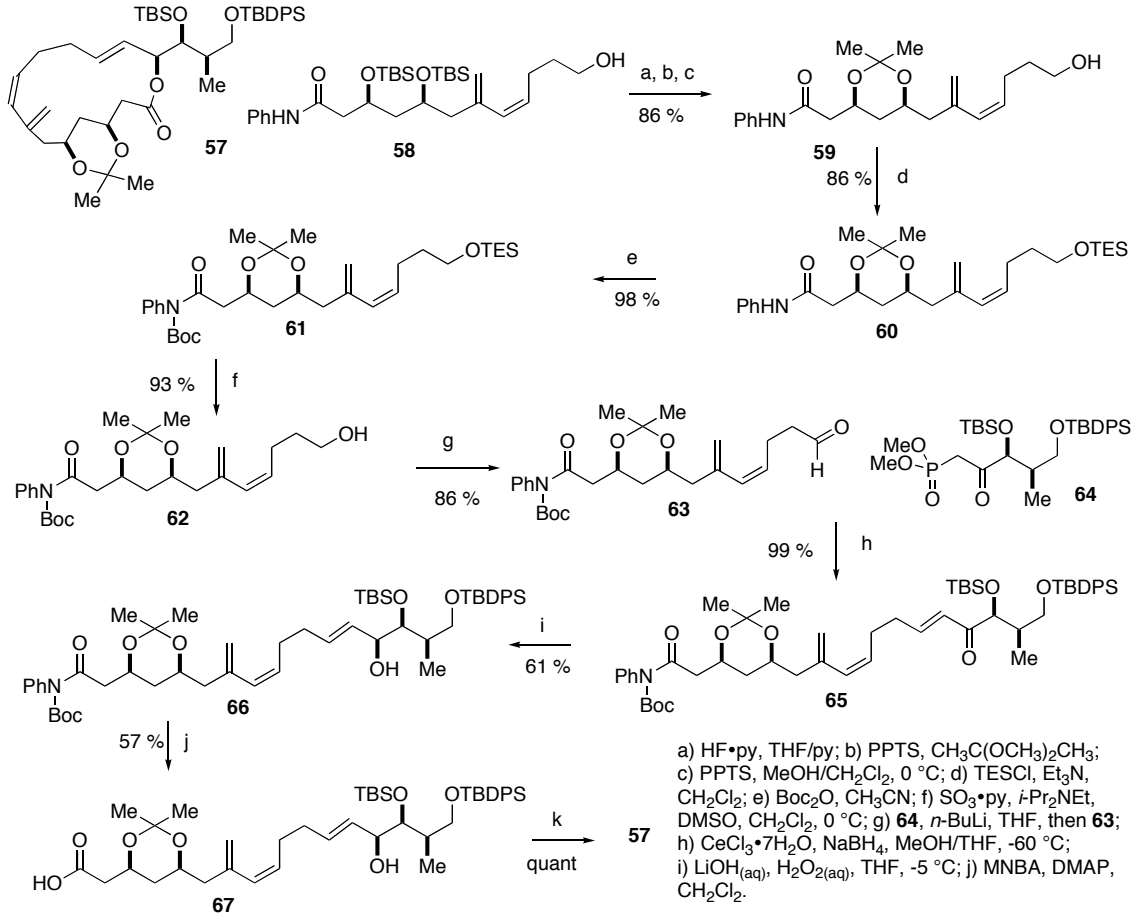
a) Trace quantities of non rearranged macrolactone may be present. Future investigation warrented

## V. Studies on $C_3$-$C_5$ Acetonide Macrolactones

With the finding that a trans-lactonization was occurring, a new protecting group strategy was briefly investigated, that is placing an acetonide on the $C_3$ and $C_5$ alcohols to form model *Z* diene **57** (Scheme 6.5). Removal of an acetonide may be done under milder conditions than the removal of TBS groups. It was envisioned that the TBS groups could be removed using a basic fluoride source, followed by mild acid treatment to remove the acetonide.[28]

(28) If the conditions to remove the acetonide still promote lactonization, a cyclopentylidene ketal may be considered as the rate of hydrolysis is even faster. See: Evans, D. A.; Connell, B. T. **2003**, *125*, 10899-10905.

**Scheme 6.5**

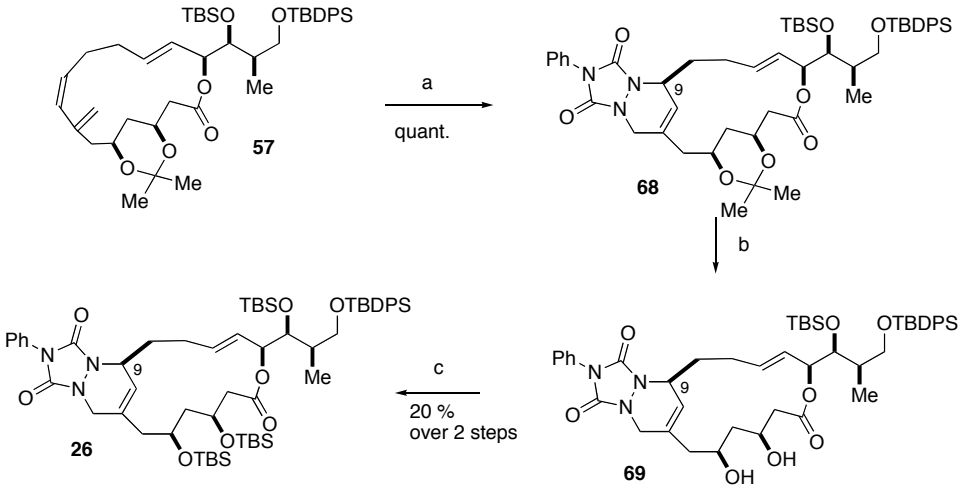



Synthesis of **57** was uneventful. Diene **58**, synthesized by Dr. Pascal Bindschädler, was desilylated with HF•py. Formation of the $C_5$ lactone was noted as a minor byproduct even with a $C_1$ amide, so the compound was protected as the acetonide without further purification. Removal of the $C_{12}$ methoxypropyl group, formed during the acetonide protection, gave compound **59**. It was noted that approximately 10% isomerization to the *E* diene occurred during the course of these reactions, and this compound was inseperable. TES protection at $C_{12}$ gave **60** which was then Boc protected to give **61**. Removal of the $C_{12}$ TES gave alcohol **62**, which was then oxidized to aldehyde **63** and combined with phosphonate **64**, available from the work in Chapter 5, to give HWE adduct **65**. Compound **65** was subject to a Luche reduction to give allylic alcohol **66**, which was complicated by the fact that the product and the starting material were

indistinguishable by TLC, unlike the Luche reduction on the bis TBS compound. The Boc amide on **66** could be hydrolyzed to give seco acid **67**, which was cyclized to **57** under Shiina conditions. The reactions in this sequence were only conducted one time each, and it is projected that if they were run again yields would be higher for the Luche reduction and amide cleavage.

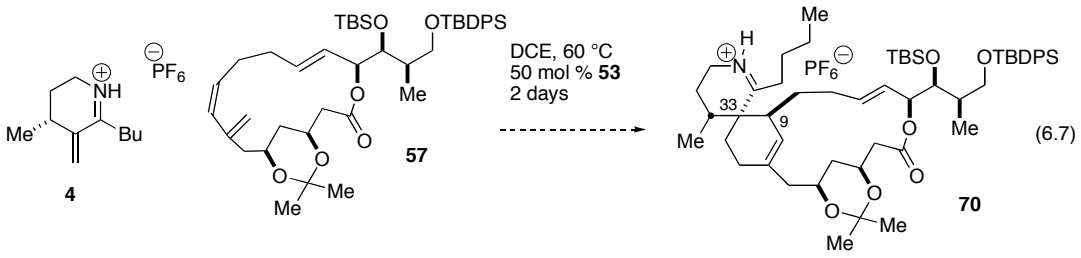
With compound **57** in hand, the first task was to assess the intrinsic facial selectivity of this molecule. Accordingly **57** was allowed to react with PTAD **25** (Scheme 6.6). The product of this reaction, **68** was obtained as predominantly one diasteromer. Notably, this reaction was slower than the PTAD reactions with compound **2**, with the colour of the PTAD persisting for up to a minute upon mixing. Unfortunately, the $^{1}$H NMR spectrum of **68** did not closely resemble those of PTAD adducts **26** or **27**, so the stereochemical assignment had to be done by a derivatization. Compound **68** was exposed to CSA in methanol which removed the acetonide without translacronization to give diol **69**.[29]

**Scheme 6.6**



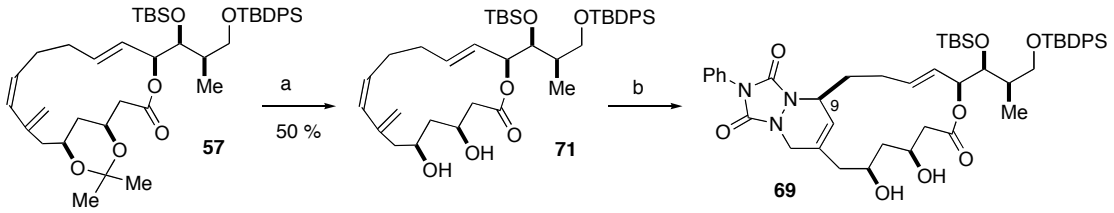

(29) This possibly represents a solution to the translactonization problem. However removal of the acetonide *before* the TBS groups precludes any assistance in lactone cleavage from hydrogen bonding by a free alcohol at $C_{15}$. More studies would have to be undertaken before this is considered a conclusive solution.

TBS protection of diol **69** gave a compound with an identical $^1$H spectrum to **26**, which suggests the desired face is exposed on the *Z* diene acetonide macrocycle. Unfortunately, compound **57** did not react with dienophile **4**. Despite extended reaction times at high temperatures, **4** and **57** could be recovered from Diels–Alder reactions unchanged (Equation 6.7). None of compound **70** was obtained. Compound **2** would have reacted or decomposed under the conditions attempted. It was noted the minor component of the *E* diene was consumed in this reaction, but nothing tractable could be obtained for characterization.




Given the slow reaction with PTAD, it was suspected that the diene may be more twisted out of an *s-cis* conformation than the diene in **2**. Accordingly an attempt was made to cleave the acetonide in **57** to make diol **71** with the hopes that an increase in the degrees of freedom would produce a more reactive diene (Scheme 6.7). Diol **71** reacted with PTAD to give predominantly compound **69**, showing that the facial selectivity was preserved. A minor compound was also noted, which suggested that comformations exposing the other face of the diene were now accessable. Unfortunately diol **71** decomposed upon reaction with compound **4**. Compound **71** was available in a small amount, and this experiment may bear repeating.

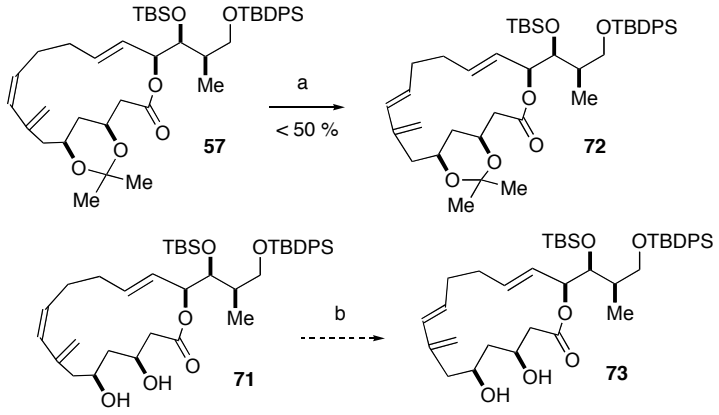
**Scheme 6.7**




a) CSA, MeOH/ $CH_2Cl_2$; b) **25**, $CDCl_3$.

One final manifestation of the reactivity difference between compound **57** and compound **2** was manifested in the isomerization behaviour. I attempted to isomerize **57** and **71** in acidic $CDCl_3$ as I had with compound **2**. Compound **57** underwent less than 50 % isomerization to compound **72** despite 4 days of continuous exposure to day/night cycles in $CDCl_3$, while compound **71** was completely stable under these conditions and none of compound **73** was obtained (Scheme 6.8).[30]

**Scheme 6.8**



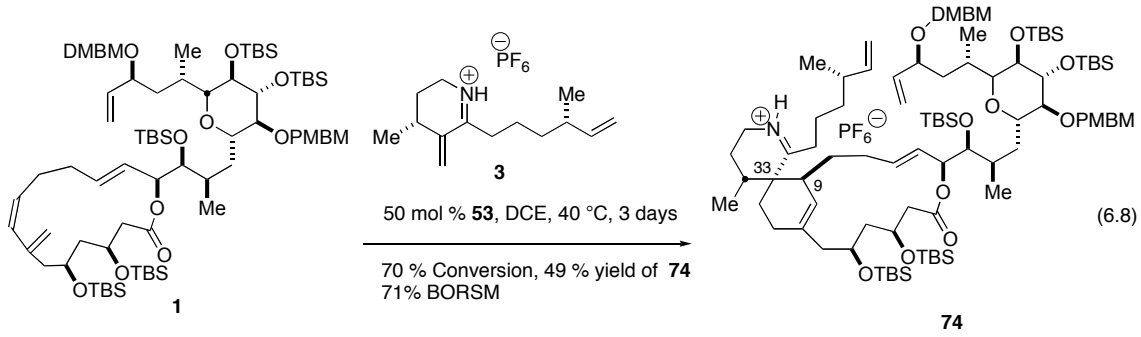

a) hν, $CDCl_3$, 4 days b) hν, $CDCl_3$, 20 days.

I believe the enhanced stability of compounds **57** and **71** relative to **2** is indicative of the diene being twisted. A consequence of this is less basic system, less ameniable to protonation and subsequent isomerization.

## VI. Diels–Alder Application to the Elaborate System and Future Outlook

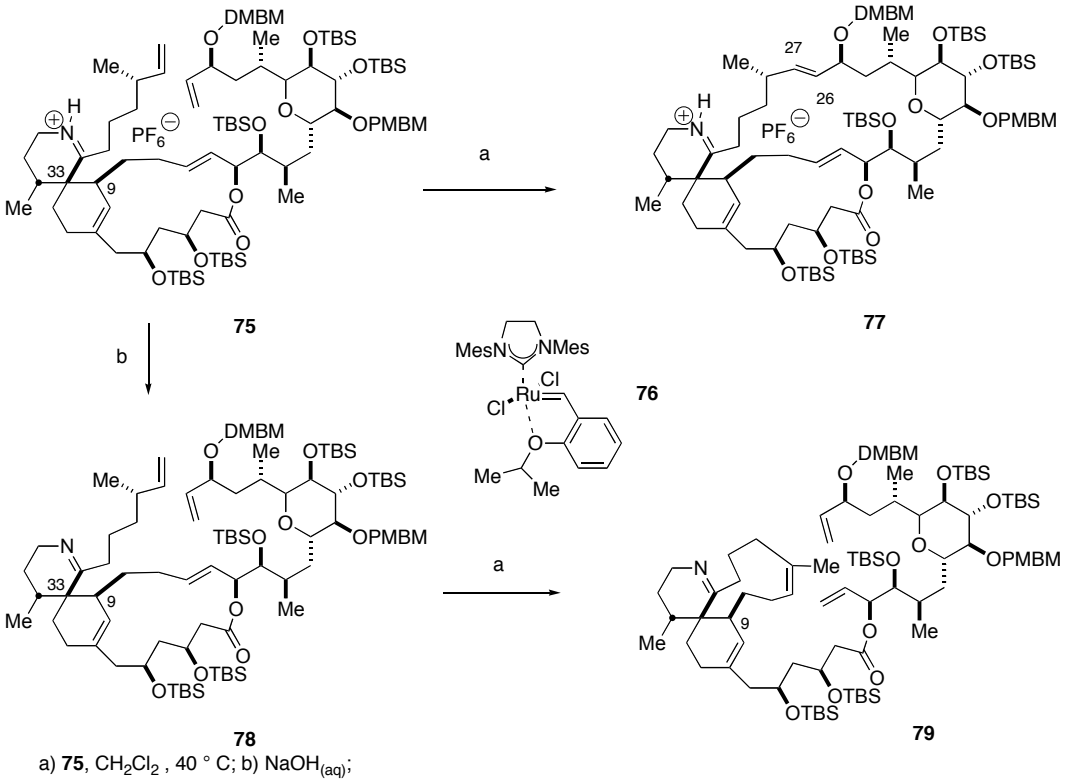
Despite trepidation about the overall protecting group strategy, since compounds **1** and **3** were in-hand, the analogous Diels–Alder was tried to produce elaborate Diels–Alder adduct **74**. What is believed to be this compound was obtained in modest yield with 9:1 diastereoselectivity. The $^1$H NMR spectrum of this compound strongly resembled that of **22** in various diagnostic regions. (Equation 6.8)

(30) The logic of continuous exposure to light was to maximize [HCl]. In retrospect, an intriguing possibility is that the reaction is undergoing photoisomerization to a photostationary state (a non- *s-cis* Z diene may be a worse chromophore). For an example of photochemistry on conjugated alkenes in acidic solvent see: Roberts, J. C.; Pincock, J. A. *J. Org. Chem*. **2004**, *69*, 4279- 4282.




Compound **75**, the isomer at $C_{33}$ was also obtained. Both compounds **74** and **75** were employed in trial RCM reactions. While these results are very preliminary, they are instructive. With this compound available, some ring closing metathesis attempts were tried. Exposure of **75**, which has undesired $C_{33}$ chemistry to second generation Hoveyda–Grubbs catalyst **76** in $C_6D_6$ or $CDCl_3$ resulted in the formation of a compound with mass corresponding to **77**, but the reactions were very unclean by $^1H$ NMR.[31]

**Scheme 6.9**




(31) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.,* **2000**, *122*, 8168-8179.

Freebase **78** was prepared, and rapidly reacted to form a compound that did not have a mass corresponding to **77**. Since the mass obtained represented the loss of $CH_2$, it was speculated that a rearrangement followed by a ring-opening reaction had occurred. The product of such a reaction could be compound **79**. There is no NMR evidence corresponding to this structure, but an interesting observation is that **79** does not streak on TLC and is far less polar than **75** or **77**.[32] This could be explained by the reluctance of the 10 membered ring in a compound such as **79** to form an *Z*-enamine tautomer (which is *E* relative to the carbon chain of the ring). Tautomerization could provide a mechanism for streaking. A mechanism for the loss of $CH_2$ is proposed where alkylidene compound **80** undergoes a protonation via a 7 membered ring to form alkylruthenium complex **81**. This could undergo b hydride elimination to form **82**.[33] A metathesis on **82** could then form compound **79** (Figure 6.12).[34]

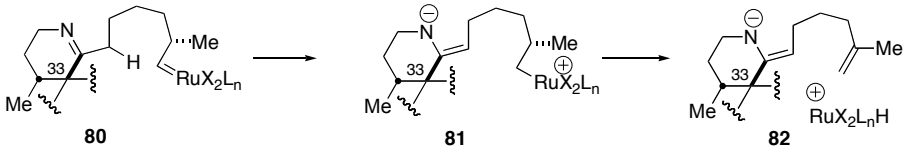



**Figure 6.12** Proposed mechanism for isomerization leading to loss of a methylene group.

With these results, attention turned to metathesis on compound **74**. Unfortunately, the same conditions that had resulted in masses consistent with RCM on compound **75** did not lead to mass hits for compound **83**. Exposure of **74** to either Hoveyda–Grubbs catalyst **76** or rapidly initiating Piers catalyst **84** in refluxing $CH_2Cl_2$ resulted in either no

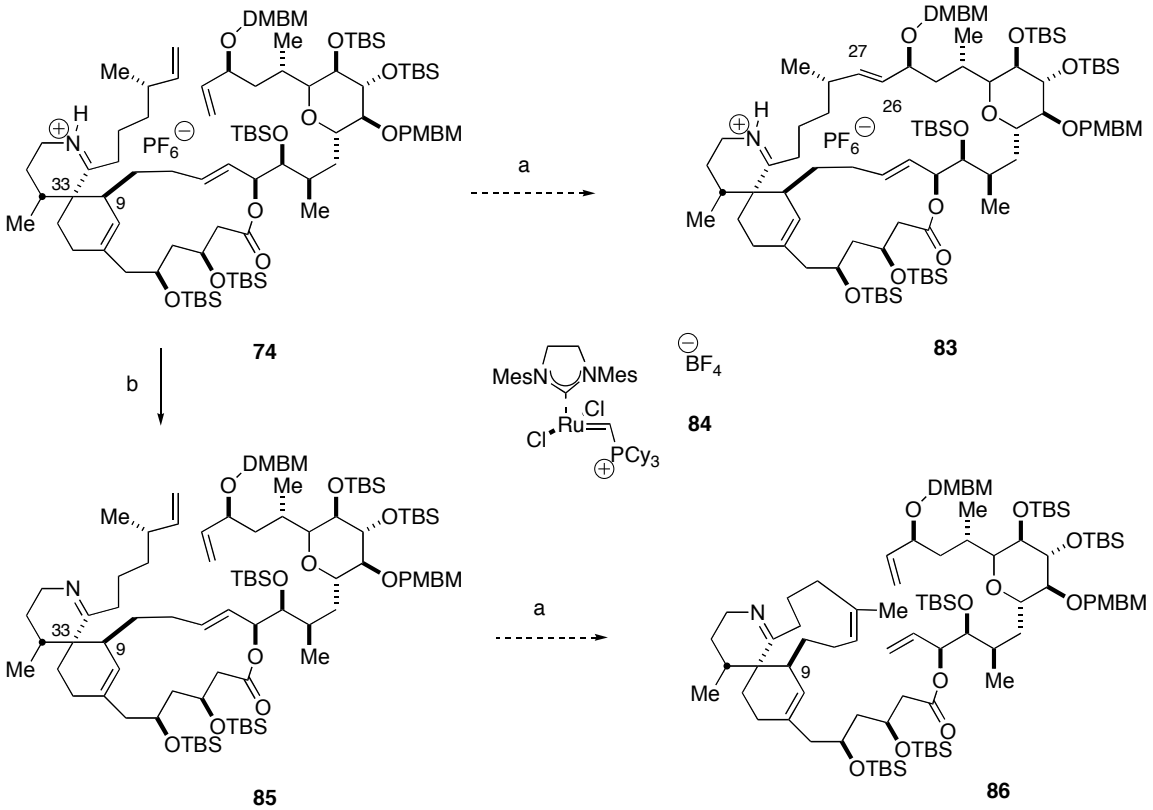
(32) **75** and **78** have the same $R_f$ on TLC in EtOAc/hexanes systems, and preperative chromatography of **53** in this solvent system results in the recovery of **56**. No loss of $HPF_6$ is observed with $MeOH/CH_2Cl_2$ systems.

(33) For a discussion of isomerization during metathesis, see: Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160- 17161.

(34) Coordination of the Ruthenium to the imine, followed by tautomerization to form a ruthenium η-3 complex may be operative.

reaction or slow decomposition of **74**.[35] Freebase **85** was prepared. This also did not undergo RCM upon exposure to catalyst **76**. Interestingly, no mass signals corresponding to compound **86** were obtained either, unlike the results obtained in Scheme 6.9. Prolonged heating in the presence of **76** resulted in complete decomposition of freebase **86**.

**Scheme 6.10**




a) **76** or **84**, $CH_2Cl_2$ , 40 °C; b) $NaOH_{(aq)}$;

An explaination for this divergent reactivity is proposed in Figure 6.13. In ruthenium alkylidene **87**, which would arise from compound **85**, the chains containing $C_{12}$ and $C_{28}$, are on the opposite faces of the ring denoted as A, while in alkylidene **88**, which arises

(35) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6161- 6165.

from **78**, the chains are on the same face of the ring denoted as A. It could be anticipated there would be a much lower barrier to forming the 10 membered ring from **88** than **87**.

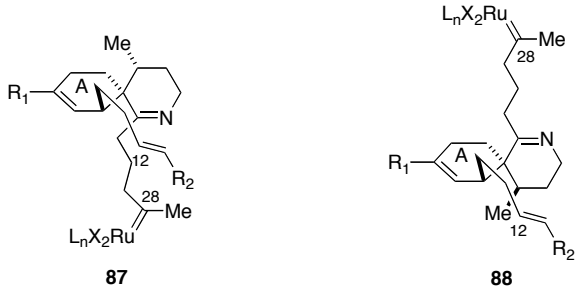



**Figure 6.13** Proposal for structural divergence in reactivity in **78** and **85**

The decomposition proposed in figure 6.12 must still happen, accounting for the distruction of **85**, however now this compound cannot undergo a by-product producing metathesis.

Two future avenues for investigation of the ring closing metathesis are proposed in Figure 6.14. The first is to synthesize ene-carbamate **89** from Diels–Alder adduct **74**.[36] This would contain a *Z* olefin (*E* relative to the 23 membered ring) that would disfavour a ring opening ring closing event. A potential danger of this substrate would be excision of the $C_{26}$ to $C_{32}$ segment if an alkylidene at $C_{26}$ engaged the ene-carbamate in a metathesis, however, the quaternary centre at $C_{33}$ should disfavour this on a steric basis. It is anticipated this compound will be more thermally stable than the iminium ions, which should allow more heating in an attempt to access conformations that close. Since this compound also lacks protic functionality, molybdenum and tungsten based catalysts could be screened.

(36) Dr. Anna Chiu was able to protect Diels–Alder adducts with the Teoc group. See Equation 1 in Appendix B of her thesis for details.

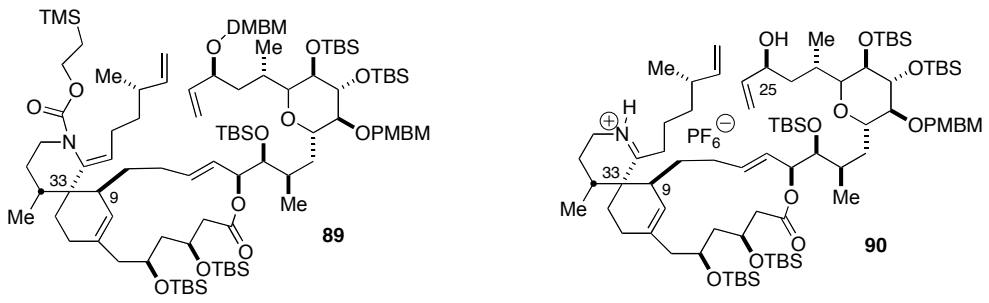



**Figure 6.14** Proposed substrate for second generation RCM reaction.

A different strategy would involve attempting to change the order in which the catalyst engages the olefins. Hoveyda has shown that the Hoveyda–Grubbs catalyst can undergo hydrogen bonding to allylic alcohols which can accelerate the rate of catalysis.[37] Deprotection of the DMBM group at the $C_{25}$ alcohol would produce compound **90** . RCM attempts on this compound would ascertain if any difference in reactivity would be present.

Completion of the synthesis would still be dependant on developing a chemoselective reduction of the $C_{26}$-$C_{27}$ olefin formed in a metathesis, followed by finding global deprotection conditions that could thwart the translactonization described above. I believe at this point, before embarking on another scale-up, a better strategy to synthesize spiro-prorocentrimine can be developed based on the observations described in this thesis. This is outlined in Appendix A.

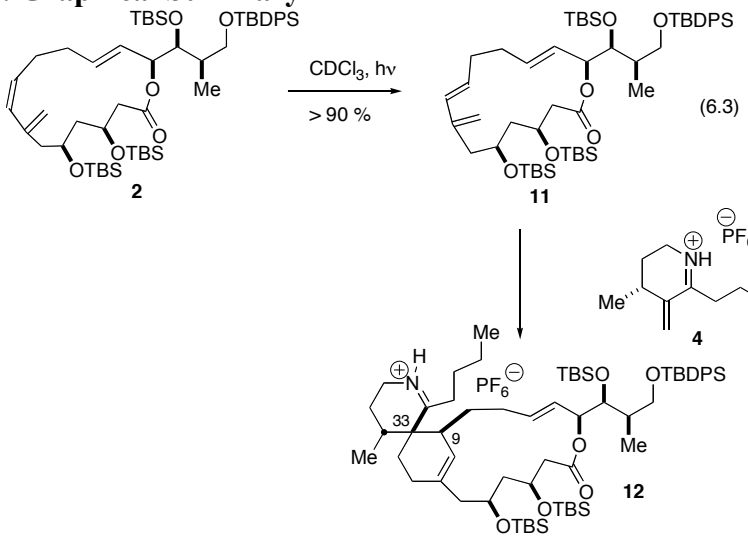
## VII. Conclusion

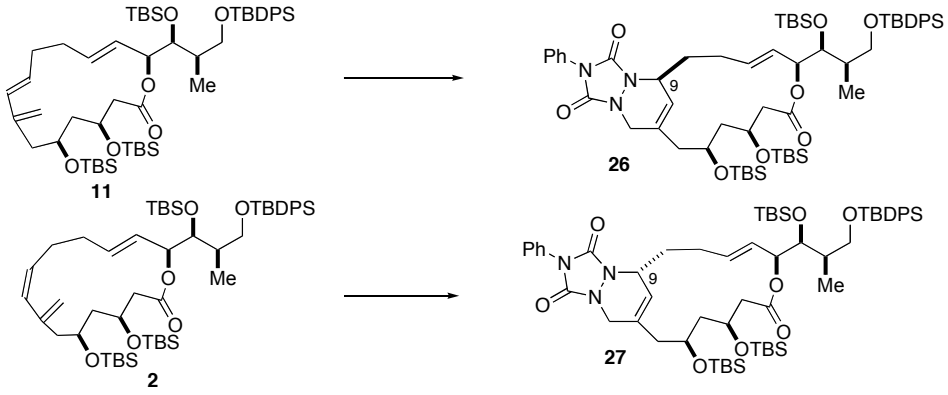
A procedure was found to isomerize the *Z* macrocyclic diene to an *E* macrocyclic diene. The *E* macrocyclic diene was found to give the same product under the standard Diels – Alder reaction conditions as the *Z* macrocyclic diene, revealing that a previously undetected olefin isomerization during the Diels–Alder reaction actually resulted in the

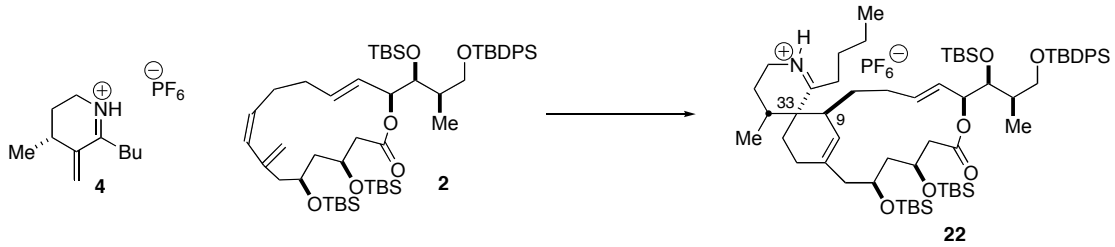
(37) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378-8379. I thank Prof. Amir Hoveyda and Dr. Robert O'Brien for suggesting this idea.

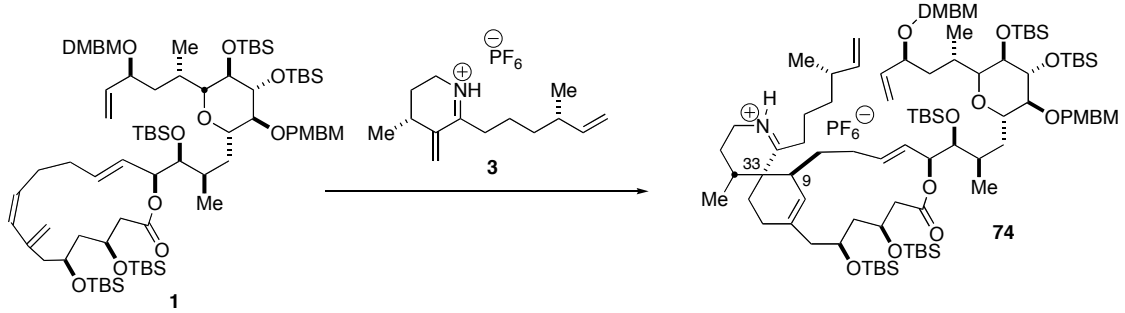
incorrect stereochemistry in previous model studies. A method to buffer the Diels–Alder reactions to prevent the isomerization based on consideration of the pKas of the conjugate acids of the dienophiles was developed and implemented. This chemistry was also applied to the elaborate system with success. Unfortunately attempts to deprotect the model system in an attempt to access a crystalline compound resulted in a contraction of the macrolactone. Protection of the alcohols at $C_3$ and $C_5$ with an acetonide was unfruitful because of a lack of reactivity of the acetonide protected *Z* diene. While future investigations could revolve around global TES protection, a proposal has been developed for a different synthesis of spiro-prorocentrimine that is described in the subsequent appendix.

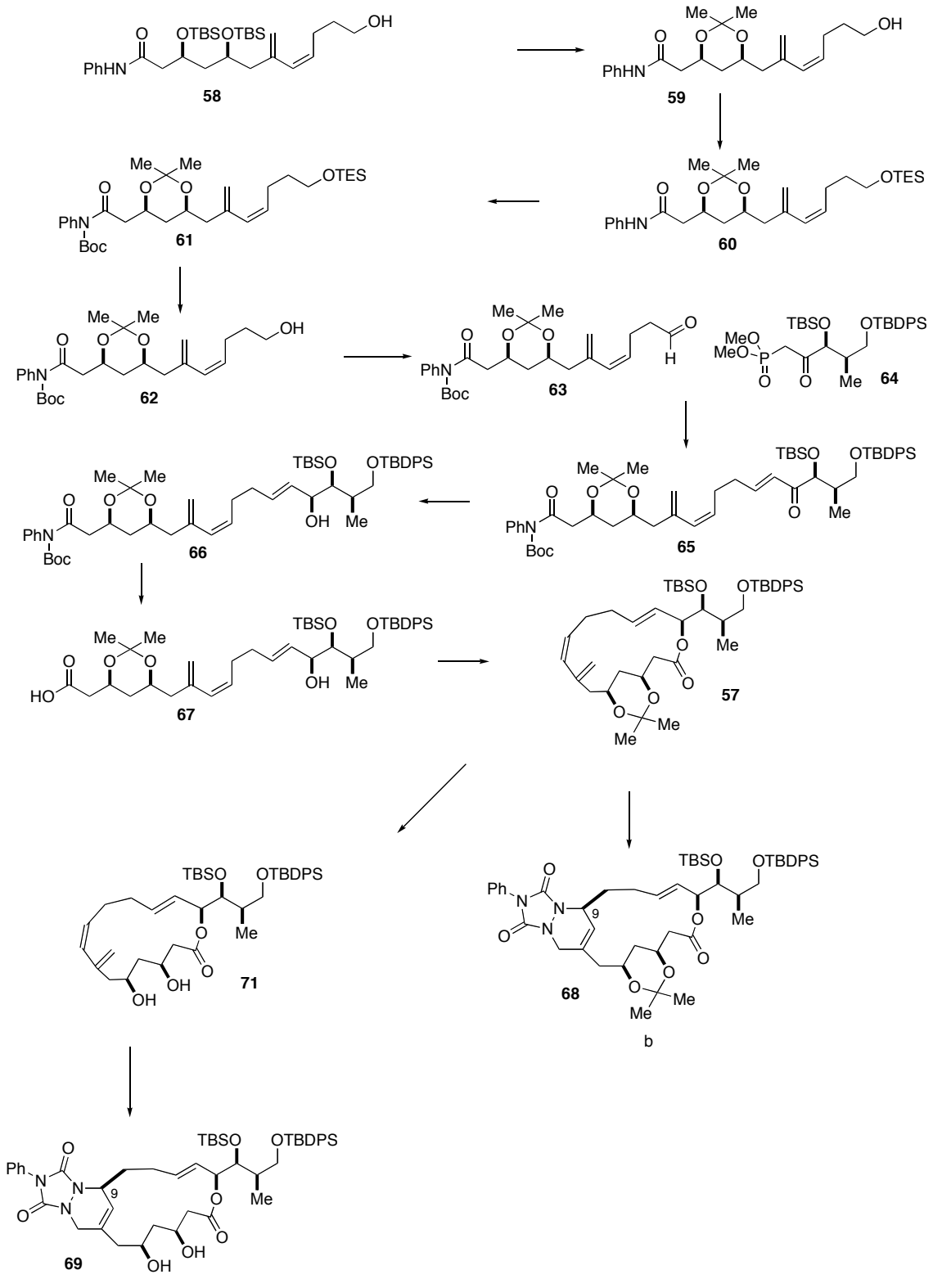
## VII. Graphical Summary

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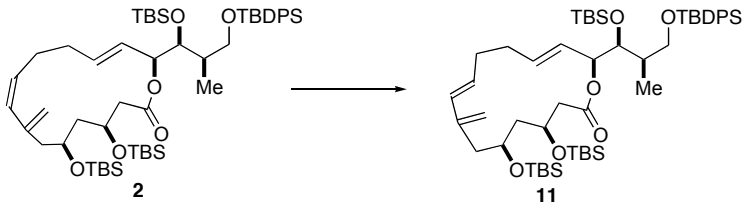
**(*E*)- TBDPS Truncated Model Macrocycle (11)**




A NMR tube containing 1 mL $CDCl_3$ and 29 mg of macrocycle **2** (0.031 mmol) was placed in direct sunlight on June 20th 2011 on the roof of the Harvard chemistry building in Cambridge Massachusetts from 9.00 am to 2.00 pm. $^1$H NMR showed approximately 20 % isomerization had occurred. The tube was then kept in the dark for 3 days, at which time $^1$H NMR showed complete isomerization to **11**. The solvent was removed to yield 29 mg of *E* macrocycle **11** as a tacky white foam, which was used without further purification.

$R_f$ = 0.85 (10 % EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -2.2 (*c* 1.24, $CHCl_3$);

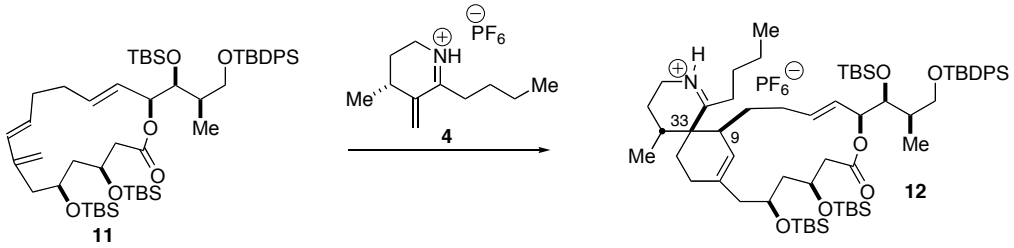
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.62 (m, 4H), 7.45- 7.33 (m, 6H), 6.04 (d, *J* = 16.2 Hz, 1H), 5.67 (dt, *J* = 14.2, 6.3 Hz, 1H), 5.53 (dt, *J* = 15.7, 6.8 Hz, 1H), 5.22 (dd, *J* = 16.6, 8.3 Hz, 1H), 5.04 (ap. t, *J* = 8.8 Hz, 1H), 4.98 (s, 1H), 4.89 (s, 1H), 4.34- 4.27 (m, 1H), 4.06 (d, *J* = 18.8 Hz, 1H), 3.74- 3.67 (m, 1H), 3.56 (t, *J* = 9.7 Hz, 1H), 3.37 (dd, *J* = 9.8, 6.3 Hz, 1H), 2.54 (td, *J* = 16.6, 2.9 Hz, 1H), 2.46 (dd, *J* = 12.8, 8.3 Hz, 1H), 2.32- 2.33 (m, 2H), 2.20- 2.11 (m, 2H), 1.79- 1.69 (m, 1H), 1.60- 1.53 (m, 1H), 1.06 (s, 9H), 0.92- 0.86 (m, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.81 (s, 9H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.15 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 170.7, 142.9, 135.6 (broad signal), 135.1, 133.9, 129.9, 129.6 (2 signals), 127.6 (broad signal), 116.7, 78.4, 71.6, 68.7, 66.4, 66.1, 47.0, 44.7, 41.8, 37.6, 30.6, 26.9, 26.0, 25.9 (2 signals), 25.8, 19.2, 18.3, 18.1, 9.1, -4.0, -4.2, -4.4, -4.5, -4.6, -4.8;

IR(film) 2928.7, 2866.1, 1736.6, 1472.6, 1263.1, 1106.6, 836.6, 775.2, 700.9 $cm^{-1}$;

Exact Mass Calc. for $C_{53}H_{90}O_6Si_4$ $[M + Na]^+$ : 957.57067 ; found : 957.5502 (ESI)

**Butyl Iminium Diels Alder with *E* diene**




*E* Macrocycle **11** (20.5 mg, 0.022 mmol, 1.0 eq) and iminium **4** (12.2 mg, 0.039 mmol, 1.8 eq) were mixed in 5 mL dry $CH_2Cl_2$, which was then removed immediately *in vacuo* to give a homogenous mixture. This was dissolved in 1 ml $CDCl_3$ from a freshly opened bottle. This mixture was held in the dark at room temperature. After 17 hours, $^1H$ NMR showed almost complete consumption of macrocycle **x**. The residue was purified by chromatography (1% MeOH in $CH_2Cl_2$) to afford 28 mg of title compound **12** (0.22 mmol, quant.) as a tan foam.

$R_f$ = 0.30 (tight spot, 10% MeOH/ $CH_2Cl_2$, faintly UV active, stains blue with CAM)

$R_f$ = 0.30 (streaks heavily, 50% EtOAc/ hexanes)

$[\alpha]^{20}_{D}$ = -23.7 (*c* 0.61 , $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 11.10 (br. s, 1H), 7.66- 7.61 (m, 4H), 7.45- 7.41 (m, 2H), 7.40- 7.34 (m, 4H), 5.85 (ddd, *J* = 9.9, 9.8, 5.0 Hz, 1H), 5.37 (s, 1H), 5.19 (dd, *J* = 8.2, 14.7 Hz, 1H), 5.07 (ap. t, *J* = 8.5 Hz, 1H), 4.10 (d, *J* = 8.6 Hz, 2H), 4.08- 4.03 (m, 1H), 3.95- 3.86 (m, 1H), 3.85- 3.77 (m, 1H), 3.56 (t, *J* = 9.7 Hz, 1H), 3.39 (dd, *J* = 10.1, 6.0 Hz, 1H), 2.73- 2.62 (m, 2H), 2.53- 2.46 (m, 3H), 2.35- 2.26 (m, 2H), 2.26- 2.18 (m, 4H), 2.07- 1.94 (m, 3H), 1.88- 1.77 (m, 3H), 1.74- 1.58 (m, 4H), 1.50 (ap. t, *J* = 10.7 Hz, 1H), 1.45- 1.33 (m, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.07 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.66 (d, *J* = 6.7 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 6H), 0.07 (s, 6H), 0.06 (s, 3H);

$^1$H NMR (600 MHz, $C_6D_6$) δ 11.50 (br. s, 1H), 7.81- 7.77 (m, 4H), 7.39- 7.27 (m, 6H), 5.91 (ddd, *J* = 15.0, 10.0, 4.8 Hz, 1H), 5.48 (br. s, 1H), 5.42 (ap. t, *J* = 8.6 Hz, 1H), 5.32 (dd, *J* = 14.9, 8.7 Hz, 1H), 4.43- 4.37 (m, 2H), 4.23- 4.18 (m, 1H), 3.86- 3.80 (m, 1H), 3.77 (t, *J* = 9.8 Hz, 1H), 3.74- 3.66 (m, 1H), 3.58 (dd, *J* = 6.0, 10.1 Hz, 1H), 2.77 (d, *J* = 13.8 Hz, 1H), 2.65 (dd, *J* = 9.7, 15.4 Hz, 1H), 2.62- 2.56 (m, 1H), 2.56- 2.49 (m, 1H), 2.42- 2.21 (m, 5H), 2.19- 2.14 (m, 1H), 1.98 (ap. t, *J* = 13.2 Hz, 1H), 1.93- 1.83 (m, 3H), 1.78- 1.67 (m, 3H), 1.58- 1.51 (m, 2H), 1.49- 1.42 (m, 2H), 1.37- 1.22 (m, 2H), 1.22 (s, 9H), 1.01 (s, 9H), 1.00 (s, 9H), 0.98 (s, 9H), 0.98- 0.94 (m, 3H), 0.92- 0.82 (m, 2H), 0.74 (d, *J* = 6.7 Hz, 3H), 0.50 (d, *J* = 6.4 Hz, 3H), 0.24 (s, 3H), 0.22 (s, 3H), 0.18 (s, 6H), 0.18 (s, 3H), 0.14 (s, 3H);

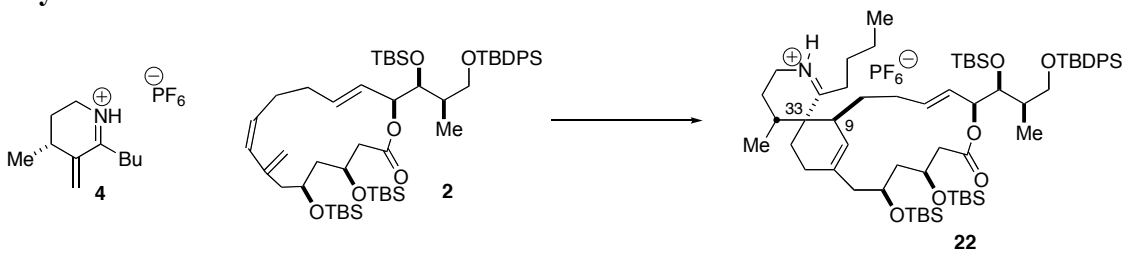
$^{13}$C NMR (125 MHz, $CDCl_3$) δ198.5, 171.1, 137.3, 136.3, 135.6 (broad signal), 133.8, 133.7, 129.7, 129.6, 128.9, 127.6 (broad signal), 126.0, 78.7, 71.1, 68.5, 67.3, 65.8, 48.7, 44.9, 44.6, 43.3, 41.2, 40.5, 37.5, 35.6, 34.8, 31.1, 29.7, 28.6, 28.1, 26.9, 26.2, 26.0, 25.9, 23.6, 22.4, 19.2, 18.3, 18.1, 17.9, 16.3, 13.3, 8.9, -4.2, -4.3, -4.4, -4.6, -4.7, -4.8;

IR(film) 2929.3, 2856.6, 1727.9, 1664.3, 1471.8, 1387.9, 1254.9, 1109.5, 974.6, 838.7, 775.0, 702.2 $cm^{-1}$;

Exact Mass Calc. for $C_{64}H_{110}NO_6Si_4^+$ [M cation]$^+$ : 1100.7405 ; found : 1100.7374 (ESI)

$^{19}F$ NMR (470 MHz, $CDCl_3$) δ -72.6 (d, $^1J_{PF}$ = 713 Hz);

**Butyl Iminium Diels Alder with Z diene**




*Z* macrocycle **2** (78 mg, 0.0833 mmol, 1 eq) and iminium **4** (77 mg, 0.250 mmol, 3.0 eq) were mixed in 1 mL DCM in a 5 mL conical flask and the solvent was immediately removed *in vacuo*. The resulting tan foam was held under high vacuum with a stir bar for 15 minutes. Subsequently, the flask was backfilled with nitrogen and 200 μL of 1,2 Dichloroethane, freshly passed through a column of 80- 200 mesh Aluminia, Basic Brockman activity 1 were added. To the solution were added 7.2 μL 3-fluoropyridine (0.0833 mmol, 1 eq). The mixture was swirled to dissolve the foam and then was sealed and placed in a 40 °C oil bath. The reaction was stirred for 132 hours, after which time the solvent was removed *in vacuo*. Analysis by $^1H$ NMR indicated a 1: 7 ratio of unconsumed Z macrocycle **2** to desired product. The ratio of desired product to undesired diastereomer was 9 : 1. The residue was redissolved in 50 mL $CH_2Cl_2$ and washed with 2x 10 mL 1.0 M $NaOH_{(aq)}$. Purification was accomplished by chromatography with 50 % EtOAc/hexanes. Macrocycle **2** (18 mg, 0.019 mmol, 23 %) was recovered. All product containing fractions were concentrated and re-dissolved in 2 mL $CH_2Cl_2$. A drop of TFA

was added and volatiles were removed *in vacuo*. The residue was taken up in 10 mL $CH_2Cl_2$ and washed 2x with saturated $NaPF_{6(aq)}$. Concentration *in vacuo* gave 52 mg of **12** (0.0417 mmol, 50 %) as a tan foam

$R_f$ = 0.30 (tight spot, 10% MeOH in $CH_2Cl_2$, stains blue with CAM, faintly UV active)
$R_f$ = 0.25 (major diastereomer, 50% EtOAc/ hexanes)

$^1$H NMR (600 MHz, $CDCl_3$) δ 10.6 (br. s, 1H), 7.67-7.63 (m, 4H), 7.46- 7.41 (m, 2H), 7.41- 7.36 (m, 4H), 5.44 (tdd, *J* = 11.8, 8.5, 2.8 Hz, 1H), 5.36 (br. s, 1H), 5.03 (dd, *J* = 15.4, 10.4 Hz, 1H), 4.81 (ap. t, *J* = 9.0 Hz, 1H), 4.08 (d, *J* = 8.8 Hz, 1H), 4.04- 3.98 (m, 1H), 3.97- 3.90 (m, 1H), 3.91- 3.84 (m, 1H), 3.65- 3.60 (m, 1H), 3.58 (ap. t, *J* = 9.6 Hz, 1H), 3.41 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.00- 2.93 (m, 1H), 2.88- 2.79 (m, 2H), 2.47- 2.32 (m, 4H), 2.26- 2.05 (m, 5H), 1.88- 1.83 (m, 1H), 1.79- 1.69 (m, 5H), 1.65 (t, *J* = 11.0 Hz, 1H), 1.56- 1.47 (m, 2H), 1.11 (d, *J* = 7 Hz, 1H), 1.09 (s, 9H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.91 (s, 3H), 0.90 (s, 9H), 0.84 (s, 9H), 0.68 (d, *J* = 6.7 Hz, 3H), 0.11 (br. s, 6H), 0.10 (s, 3H), 0.07 (s, 6H).

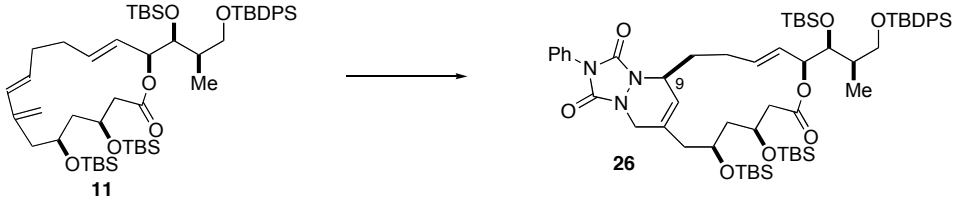
$^1$H NMR (500 MHz, $C_6D_6$) δ 10.95 (br. s, 1H), 7.82- 7.77 (m, 4H), 7.31- 7.26 (m, 6H), 5.57 (ap. t, *J* = 14.6 Hz, 1H), 5.14 (br. s, 1H), 5.05 (ap. t, *J* = 8.8 Hz, 1H), 4.99 (dd, *J* = 15.1, 9.3 Hz, 1H), 4.20 (d, *J* = 8.3 Hz, 1H), 4.15- 4.07 (m, 1H), 4.07- 3.93 (m, 2H), 3.80- 3.73 (m, 2H), 3.61- 3.58 (m, 1H), 3.05- 2.89 (m, 2H), 2.81- 2.75 (m, 1H), 2.62- 2.58 (m, 1H), 2.54- 2.49 (m, 1H), 2.43- 2.38 (m, 1H), 2.25- 2.19 (m, 1H), 2.15 (dd, *J* = 12.2, 9.8 Hz, 1H), 2.05- 1.83 (m, 7H), 1.83- 1.75 (m, 1H), 1.70- 1.62 (m, 2H), 1.60- 1.52 (m, 2H), 1.19 (s, 9H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.04 (s, 9H), 0.98 (s, 9H), 0.91 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.18 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H).

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 198.8, 170.5, 135.6 (broad signal), 135.1, 133.8 (broad signal), 129.7, 129.6, 128.0, 127.6, 122.6, 80.9, 70.9, 68.8, 67.0, 65.9, 47.3, 46.8, 46.0, 45.3, 42.7, 39.1, 37.4, 33.3, 29.7, 28.9, 28.5, 28.4, 28.1, 26.9, 26.1, 26.0, 25.9, 25.8, 24.6, 22.4, 19.2, 18.4, 18.0, 17.2, 13.3, 9.0, -3.9, -4.0, -4.5, -4.6;

IR(film) 3344.8, 3290.4, 2955.6, 2856.9, 1720.7, 1671.8, 1471.8, 1387.2, 1255.2, 1109.9, 838.7, 775.1, 702.4 $cm^{-1}$;

Exact Mass Calc. for $C_{64}H_{110}NO_6Si_4^+$ [M cation]$^+$ : 1100.7405 ; found : 1100.7517 (ESI)

**PTAD Diels- Alder with E diene**




*E* macrocycle **11** (13 mg, 0.014 mmol) was dissolved in 2 mL $CH_2Cl_2$. Separately PTAD (2.4 mg, 0.014 mmol, 1 eq) was dissolved in 1 mL $CH_2Cl_2$. The cherry red PTAD solution was added dropwise to the solution of **11** and the red colour was discharged with each drop. At the very end of the addition, a faint pink colour persisted. The solvent was removed and 1H NMR analysis showed essentially one diastereomer. The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford Diels- Alder adduct **26** (15 mg, 0.013 mmol, 97%) as a clear colourless oil.

Rf = 0.16 (10% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -50.8 (*c* 0.34, $CHCl_3$);

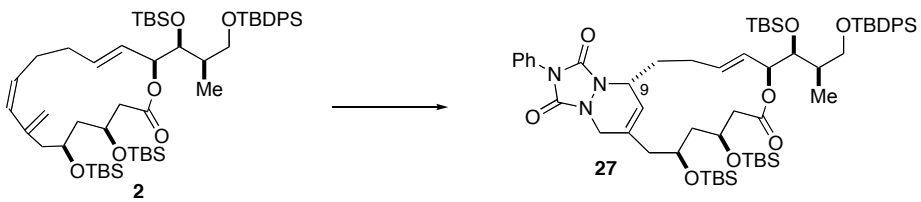
$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.64 (ap. t, *J* = 6.7, 4H), 7.54 (ap d, *J* = 7.5 Hz, 2H), 7.46 (ap. t, *J* = 7.6 Hz, 2H), 7.45- 7.40 (m, 2H), 7.40- 7.34 (m, 5H), 5.89 (ddd, *J* = 10.4, 10.3, 4.8 Hz, 1H), 5.49 (br. s, 1H), 5.24 (dd, *J* = 16.1, 9.2 Hz, 1H), 5.11 (ap. t, *J* = 9.1 Hz, 1H), 4.28- 4.23 (m, 2H), 4.17 (ap. t, *J* = 8.9 Hz, 1H), 4.12 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.09- 4.04 (m, 1H), 3.98 (d, *J* = 16.2 Hz, 1H), 3.57 (t, *J* = 9.8 Hz, 1H), 3.39 (dd, *J* = 10.2, 5.1 Hz, 1H), 2.59- 2.49 (m, 2H), 2.45- 2.23 (m, 4H), 1.81- 1.70 (m, 2H), 1.65- 1.56 (m, 2H), 1.07 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.84 (s, 9H), 0.64 (d, *J* = 6.4 Hz, 3H), 0.10 (br. s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.5, 152.1, 137.7, 135.6, 133.8, 131.4, 129.8, 129.6, 129.1, 127.9, 127.7, 127.6, 127.1, 126.7, 125.3, 124.6, 79.2, 70.9, 68.4, 67.0, 65.7, 55.5, 47.5, 44.3, 43.3, 38.5, 37.4, 36.6, 31.6, 31.4, 29.7, 26.9, 26.0, 25.9, 25.8, 25.7, 24.7, 19.2, 18.3, 18.1, 17.9, 8.7, -4.2, -4.3, -4.5, -4.7 (2 signals);

IR(film) 2954.9, 2956.4, 1775.4, 1720.5, 1503.6, 1471.5, 1415.7, 1255.9, 1090.3, 836.7, 775.2, 702.0 $cm^{-1}$;

Exact Mass Calc. for $C_{61}H_{95}N_3O_8Si_4$ $[M + Na]^+$ : 1132.6088 ; found : 1132.5877 (ESI)

**PTAD Diels- Alder with Z diene**




The integrity of the Z diene in the sample of macrocycle used in this experiment was investigated by $^{1}$H NMR immediately prior to the experiment and a 33: 1 ratio of *Z* to *E*

dienes was observed. Z macrocycle **2** (9 mg, 0.01 mmol, 1 eq) was dissolved in 1 mL $CH_2Cl_2$ and a solution of PTAD (1.7 mg, 0.01 mmol, 1 eq) was added dropwise until a faint pink colour persisted. The solvent was removed *in vacuo* and $^1$H NMR analysis showed a 6:1 ratio of disastereomers where the minor distereomer corresponds to compound **26** . The diastereomers can be separated by gradient chromatography (5% to 10% EtOAc/ hexanes). Characterization data for the major diastereomer **27**:

Rf = 0.13 (10% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +73 (*c* 0.66, $CHCl_3$);

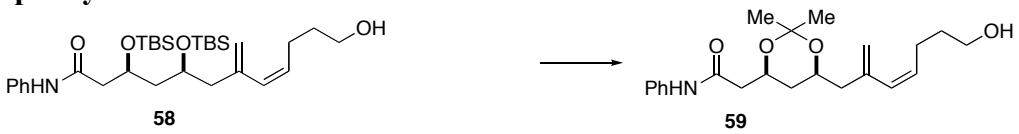
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.66- 7.62 (m, 4H), 7.55 (ap. d, *J* = 9.4 Hz, 2H), 7.49- 7.34 (m, 9H), 5.79 (ap. dt, *J* = 15.4, 7.0 Hz, 1H), 5.71 (ap. d, *J* = 4.8 Hz, 1H), 5.41 (dd, *J* = 15.4, 6.9 Hz, 1H), 5.09 (ap. t, *J* = 7.8 Hz, 1H), 4.71 (d, *J* = 16.4 Hz, 1H), 4.42- 4.37 (m, 1H), 4.14- 4.10 (m, 1H), 4.08 (d, *J* = 8.5 Hz, 1H), 3.80 (d, *J* = 16.4 Hz, 1H), 3.58 (ap. t, *J* = 9.4 Hz, 1H), 3.40 (dd, *J* = 10.2, 6.1 Hz, 1H), 2.58 (AB dd, *J* = 15.2, 2.9 Hz, 1H), 2.51 (AB dd, *J* = 15.2, 10.3 Hz, 1H), 2.39 (d, *J* = 13.8 Hz, 1H), 2.38- 2.30 (m, 2H), 2.26 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.16- 2.11 (m, 1H), 1.95 – 1.87 (m, 1H), 1.79- 1.68 (m, 2H), 1.62- 1.56 (m, 2H), 1.07 (s, 9H), 0.94 (s, 9H), 0.92 (s, 9H), 0.85 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.8, 152.4, 151.5, 135.6, 134.1, 133.8 (2 signals), 131.4, 129.7, 129.6, 129.0, 128.6, 127.9, 127.6, 126.8, 125.3, 124.6, 77.8, 71.9, 68.5, 67.3, 65.8, 54.8, 47.9, 44.0, 43.4, 37.7, 37.6, 36.6, 34.3, 30.1, 26.9, 26.0, 25.9, 25.8, 24.7, 19.2, 18.3, 18.1, 17.9, -4.2, -4.4, -4.5, -4.6 (2 signals), -4.7;

IR(film) 2928.7, 2856.1, 1772.4, 1719.0, 1502.4, 1471.9, 1412.9, 1255.1, 1091.5, 836.9, 775.2, 702.0 $cm^{-1}$;

Exact Mass Calc. for $C_{61}H_{95}N_3O_8Si_4$ $[M + Na]^+$ : 1132.6088 ; found : 1132.5980 (ESI)

**2-((4*S*,6*S*)-6-((*Z*)-7-hydroxy-2-methylenehept-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-*N*-phenylacetamide**




**58** **59**

The following telescoping sequence was found to give optimum throughput. The terminal MOP group is not entirely stable to chromatography, but relying on chromatography for its removal proved detrimental to yields. Accordingly the following 3 step procedure is implemented:

Z diene **58** (156 mg, 0.278 mmol) was dissolved in 5 mL THF in a Falcon® tube and 0.6 mL pyridine were added followed by 0.8 mL HF-pyridine. The mixture was stirred for 18 hours, until no species that stained in CAM with an $R_f$ greater than 0.05 in 70% EtOAc/hexanes were present. The reaction was quenched by the addition of solid $NaHCO_3$ and stirred until bubbling ceased (approximately 15 minutes). The mixture was filtered through Celite®, and washed with 40 mL EtOAc. The solvent was removed *in vacuo* and the residue was held under high vacuum for 2 hours to remove residual pyridine. The residue was used directly in the next step without any further purification.

TLC characterization of intermediate triol:

$R_f$ = 0.05 (70% EtOAc/hexanes, faintly UV active, stains dark blue in CAM)

The crude triol was dissolved in 3 mL $CH_2Cl_2$ and 1.5 ml dimethoxypropane were added. To the stirring solution at room temperature was added a crystal of PPTS. After several minutes, an spot with $R_f$ = 0.4 in 70% EtOAc/hexanes was observed. This was attributed to methoxypropyl protection of the primary alcohol. Over the next hour, this turned into a spot with $R_f$ = 0.95 in 70% EtOAc/hexanes, which was attributed to the addition of the acetonide group. After 1.5 hours, when the lower spot vanished, the reaction was quenched with 2 mL saturated $NaHCO_{3(aq)}$ and the aqueous layer was extracted with 10 mL DCM. The combined organic layers were dried with brine and $Na_2SO_4$ then concentrated to yield a crude MOP acetonide that was used directly in the next step.

TLC characterization of intermediate MOP acetonide:

Rf = 0.95 (70% EtOAc/hexanes. UV active, stains blue in CAM)

The crude acetonide was dissolved in a mixture of 3 mL $CH_2Cl_2$ and 0.6 mL MeOH and cooled to 0 °C. A crystal of PPTS was added. After 2.5 hours, TLC (70% EtOAc/hexanes) showed consumption of the starting material, so the reaction was quenched with saturated $NaHCO_{3(aq)}$ and diluted with 40 mL 90% EtOAc/hexanes. This was dried with brine, then over $Na_2SO_4$, then concentrated *in vacuo*. The residue was purified by flash chromatography (50% EtOAc/hexanes) to yield 59.4 mg of alcohol **59** (0.159 mmol, 57% ) as a clear colourless oil.

$R_f$ = 0.60 (70% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -5.5 (*c* 2.97, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 8.39 (br. s, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.80 (dd, *J* = 11.7, 1.3 Hz, 1H), 5.50 (dt, *J* = 11.6, 7.4

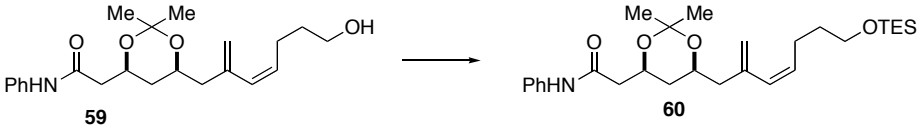
Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 4.30- 4.25 (m, 1H), 4.00- 3.95 (m, 1H), 3.65 (AB d, *J* = 6.0 Hz, 1H), 3.63 (AB d, *J* = 6.1 Hz, 1H), 2.58- 2.50 (m, 2H), 2.40 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.33 (pent. d, *J* = 7.8, 1.5 Hz, 1H), 2.29 (pent. d, *J* = 6.7, 1.4 Hz, 1H), 2.15 (dd, *J* = 13.7, 7.2 Hz, 1H), 1.69- 1.62 (m, 2H), 1.53- 1.48 (m, 2H), 1.49 (s, 6H), 1.28 (dd, *J* = 11.6, 14.5 Hz, 1H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 169.0, 140.6, 137.9, 132.0, 130.1, 128.9, 124.0, 119.6, 116.4, 99.1, 67.7, 66.6, 62.0, 43.9 (2 signals), 35.6, 32.8, 30.1, 24.9, 19.8;

IR(film) 3458.1, 3310.7, 3138.8, 2993.1, 2939.2, 1665.3, 1600.1, 1548.1, 1499.3, 1444.2, 1380.3, 1259.8, 1200.3, 1167.1, 1063.0, 984.7, 900.8, 756.3, 692.6 $cm^{-1}$ ;

Exact Mass Calc. for $C_{22}H_{31}NO_4$ $[M + Na]^+$ : 374.2326 ; found : 374.2336 (ESI)

**2-((4*S*,6*S*)-2,2-dimethyl-6-((*Z*)-2-methylene-7-((triethylsilyl)oxy)hept-3-en-1-yl)-1,3-dioxan-4-yl)-*N*-phenylacetamide**




Alcohol **59** (59 mg, 0.158 mmol, 1 eq) was dissolved in 3 mL $CH_2Cl_2$ and DMAP (4 mg, 0.2 eq) and triethylamine (0.110 mL, 0.790 mmol, 5 eq) were added. To the solution were added 0.080 mL (0.474 mmol, 3 eq) of chlorotriethylsilane. After 5 minutes, TLC analysis (20% EtOAc/hexanes) showed completion. The reaction was quenched with saturated $NaHCO_{3(aq)}$, diluted with 50 mL $CH_2Cl_2$ and washed with 10 ml saturated $NaHCO_{3(aq)}$. The organic layer was washed with brine, dried over $Na_2SO_4$ and

concentrated *in vacuo*. Purification of the residue by flash chromatography afforded 67.2 mg of TES ether **60** (0.137 mmol, 87%) as a clear colourless oil.

$R_f$ = 0.30 (20% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -1.9 (*c* 3.36, $CHCl_3$);

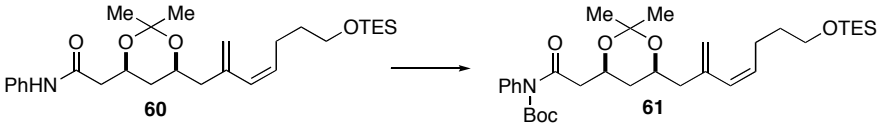
$^1$H NMR (600 MHz, $CDCl_3$) δ 8.46 (br. s, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 5.77 (dd, *J* = 11.6, 1.0 Hz, 1H), 5.51 (dt, *J* = 11.7, 7.3 Hz, 1H), 5.04 (s, 1H), 4.94 (s, 1H), 4.30- 4.25 (m, 1H), 3.99- 3.95 (m, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.58- 2.49 (m, 2H), 2.40 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.26 (qd, *J* = 7.6, 1.6 Hz, 2H), 2.15 (dd, *J* = 13.8, 6.8 Hz, 1H), 1.61 (ap. pent., *J* = 7.8 Hz, 2H), 1.59- 1.54 (dt, *J* = 13.2, 2.3 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.29 (q, *J* = 12.8 Hz, 1H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 168.8, 140.7, 138.1, 132.4, 129.6, 128.9, 123.9, 119.5, 116.2, 99.1, 67.7, 66.6, 62.3, 44.0, 35.6, 33.2, 30.2, 25.2, 19.8, 6.7, 4.4;

IR(film) 3313.3, 2992.3, 2952.3. 2942.3, 2875.8, 1654.3, 1600.5, 1546.4, 1499.4, 1443.6, 1380.0, 1258.5, 1200.2, 1167.7, 1099.7, 1016.3, 898.7, 810.7, 746.9 $cm^{-1}$ ;

Exact Mass Calc. for $C_{28}H_{45}NO_4Si$ $[M + Na]^+$ : 510.30101 ; found : 510.3017 (ESI)

***tert*-butyl (2-((4*S*,6*S*)-2,2-dimethyl-6-((*Z*)-2-methylene-7-((triethylsilyl)oxy)hept-3-en-1-yl)-1,3-dioxan-4-yl)acetyl)(phenyl)carbamate**




Amide **60** (67 mg, 0.137 mmol, 1 eq) was dissolved in 3 mL $CH_2Cl_2$ and DMAP (84 mg, 0.687 mmol, 5 eq) and $BOC_2O$ (149 mg, 0.687 mmol, 5 eq) were added. After 2 hours, TLC (20% EtOAc/hexanes, CAM) showed complete consumption of the starting material. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (10% EtOAc/hexanes) to yield 78.8 mg of Boc amide **61** (0.134 mmol, 98%) as a clear colourless oil.

$R_f$ = 0.60 (20% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +3.5 (*c* 3.94, $CHCl_3$);

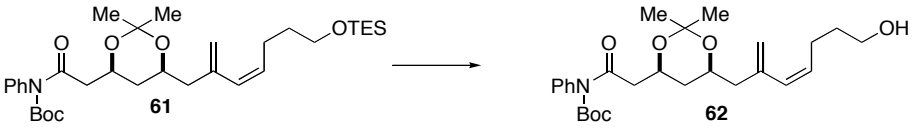
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.39 (ap. t, *J* = 8.7 Hz, 2H), 7.33 (ap.t, *J* = 7.5 Hz, 1H), 7.08 (ap. d, *J* = 7.3 Hz, 2H), 5.78 (dd, *J* = 11.6, 1.0 Hz, 1H), 5.50 (dt, *J* = 11.7, 7.3 Hz, 1H), 5.04 (s, 1H), 4.93 (s, 1H), 4.45- 4.40 (m, 1H), 3.99- 3.94 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.20 (dd, *J* = 17.0, 7.3 Hz, 1H), 2.95 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.40 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.27 (qd, *J* = 7.5, 1.6 Hz, 2H), 2.14 (dd, *J* = 13.7, 7.0 Hz, 1H), 1.65-1.59 (m, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.38 (s, 9H), 1.21 (q, *J* = 12.5 Hz, 1H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ173.0, 152.6, 141.1, 138.8, 132.1, 129.8, 128.9, 128.1, 127.7, 115.9, 98.7, 83.0, 67.7, 66.0, 62.4, 44.6, 44.2, 36.4, 33.3, 30.1, 27.7, 25.1, 19.6, 6.7, 4.4;

IR(film) 2952.7, 2876.2, 1737.4, 1707.8, 1457.4, 1369.9, 1294.0, 1256.1, 1090.1, 745.8 $cm^{-1}$ ;

Exact Mass Calc. for $C_{33}H_{43}NO_6Si_4$ $[M + Na]^+$ : 610.35344 ; found : 610.3551 (ESI)

***tert*-butyl (2-((4*S*,6*S*)-6-((*Z*)-7-hydroxy-2-methylenehept-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetyl)(phenyl)carbamate**




TES ether **61** (78.8 mg, 0.134 mg) was dissolved in a mixture of 3 mL $CH_2Cl_2$ and 0.6 mL MeOH. This mixture was cooled to 0 °C and a crystal of PPTS was added. TLC after 15 minutes (20% EtOAc/hexanes) showed complete consumption of starting material so the reaction was quenched with 1 mL saturated $NaHCO_{3(aq)}$. This was diluted with 30 mL 90% EtOAc/hexanes, washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo* to yield a residue. Purification by flash chromatography (40% EtOAc/hexanes) yielded 58.2 mg of alcohol **62** (0.123 mmol, 92%) as a clear colourless oil.

$R_f$ = 0.15 (40% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -9.0 (*c* 2.91, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.41- 7.37 (m, 2H), 7.35- 7.31 (m, 1H), 7.09- 7.06 (m, 2H), 5.80 (d, *J* = 11.6 Hz, 1H), 5.49 (dt, *J* = 11.6, 6.9 Hz, 1H), 5.06 (s, 1H), 4.93 (s, 1H),

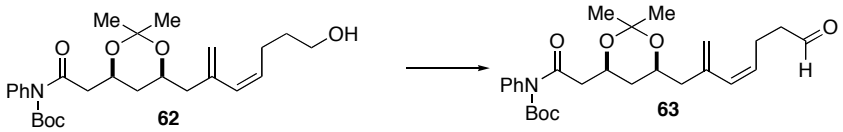
4.42- 4.36 (m, 1H), 3.98- 3.92 (m, 1H), 3.60- 3.56 (m, 2H), 3.18 (dd, *J* = 17.3, 6.6 Hz, 1H), 2.97 (dd, *J* = 17.2, 6.0 Hz, 1H), 2.42 (dd, *J* = 13.5, 5.6 Hz, 1H), 2.36 (pent. d, *J* = 8.0, 1.3 Hz, 1H), 2.27- 2.18 (m, 1H), 2.14 (dd, *J* = 13.6, 7.8 Hz, 1H), 1.72- 1.67 (m, 1H), 1.66- 1.60 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.37 (s, 9H), 1.16 (q, *J* = 11.8 Hz, 1H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 152.4, 140.9, 138.7, 132.0, 130.1, 128.9, 128.1, 127.8, 116.2, 98.7, 83.2, 67.8, 66.0, 62.2, 44.6, 44.2, 36.3, 32.9, 30.1, 27.7, 24.9, 19.7;

IR(film) 3484.1, 2990.4, 2938.4, 1737.2, 1370.2, 1293.8, 1257.8, 1154.8, 1089.4, 758.2, 694.4;

Exact Mass Calc. for $C_{27}H_{39}NO_6$ $[M + Na]^+$ : 496.2670 ; found : 496.2681 (ESI)

***tert*-butyl (2-((4*S*,6*S*)-2,2-dimethyl-6-((*Z*)-2-methylene-7-oxohept-3-en-1-yl)-1,3-dioxan-4-yl)acetyl)(phenyl)carbamate**




Alcohol **62** (60 mg, 0.127 mmol, 1eq) was dissolved in $CH_2Cl_2$ and cooled to 0 °C. Hunig's base (0.070 mL, 0.380 mmol, 3 eq) was added, followed by DMSO (0.053 mL, 0.760 mmol, 6 eq). $SO_3$-Py complex (40 mg, 0.253 mmol, 2 eq) was added, and TLC (40% EtOAc/hexanes) after 10 minutes showed the completion of the reaction. Volatiles were removed *in vacuo* and the residue was purified by flash chromatography (20% EtOAc/hexanes) to yield aldehyde **63** (50.1 mg, 0.106 mmol, 83%) as a clear colourless oil.

$R_f$ = 0.25 (20% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_{D}$ = +1.6 (*c* 2.50, $CHCl_3$);

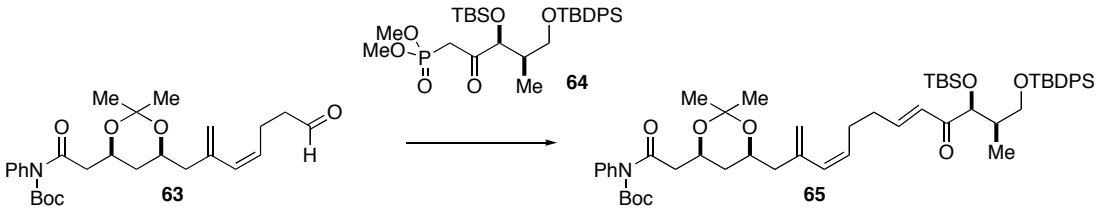
$^1$H NMR (600 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.4 Hz, 1H), 7.39- 7.36 (m, 2H), 7.33- 7.30 (m, 1H), 7.09- 7.06 (m, 2H), 5.83 (d, *J* = 11.6, 1H), 5.46- 5.41 (m, 1H), 5.08 (s, 1H), 4.91 (s, 1H), 4.44- 4.38 (m, 1H), 4.38- 4.32 (m, 1H), 3.20 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.96 (dd, *J* = 7.3, 4.4 Hz, 1H), 2.38 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.14 (dd, *J* = 13.8, 4.9 Hz, 1H), 1.64 (dt, *J* = 12.8, 2.3 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.36 (s, 9H), 1.19 (q, *J* = 11.6 Hz, 1H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.7,173.0, 152.9, 140.9, 138.8, 131.2, 129.8, 128.9 (2 peaks), 128.1, 127.7, 116.4, 98.7, 83.1, 67.7, 66.0, 44.6, 44.1, 43.9, 36.4, 30.1, 27.7, 21.3, 19.6;

IR(film) 2989.4, 2939.3, 1736.1, 1493.2, 1379.6, 1294.1, 1257.7, 1199.1, 1155.3, 1088.2, 756.6, 694.5 $cm^{-1}$;

Exact Mass Calc. for $C_{27}H_{37}NO_6$ $[M + Na]^+$ : 494.2513 ; found : 494.2507 (ESI)

***tert*-butyl (2-((4*S*,6*S*)-6-((3*Z*,7*E*,10*S*,11*R*)-10-((*tert*-butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-11-methyl-2-methylene-9-oxododeca-3,7-dien-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetyl)(phenyl)carbamate**



Phosphonate **64** (126 mg, 0.213 mmol, 2.0 eq) was dissolved in 1 mL THF and cooled to 0 °C. Freshly titrated nBuLi (45 μL, 3.5 M, 0.16 mmol, 1.5 eq) was added dropwise and the clear colourless solution was stirred for 25 minutes. A solution of aldehyde **63** (50.1 mg, 0.106 mol, 1 eq) in 1 + 1 mL THF was added and the reaction was protected from light. The cooling bath was allowed to decay naturally over 2 hours. After 20 hours, TLC (20% EtOAc/hexanes, CAM visualization) indicated consumption of the aldehyde, so the reaction was quenched by addition of saturated $NH_4Cl_{(aq)}$ and diluted with 40 mL 90% EtOAc/hexanes. This was washed with brine, then dried over $Na_2SO_4$. Concentration *in vacuo* gave a residue that was purified by flash chromatography (20% EtOAc/hexanes) to afford 98.8 mg (0.105 mmol, 99%) of enone **65** as a very pale yellow oil.

$R_f$ = 0.50 (20% EtOAc/hexanes, strongly UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -6.1 (*c* 4.94, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.65 (m, 4H), 7.44- 7.40 (m, 2H), 7.40- 7.36 (m, 6H), 7.33- 7.30 (m, 1H), 7.08- 7.06 (m, 2H), 6.93 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.81 (d, *J* = 14.2 Hz, 1H), 5.44 (dt, *J* = 11.6, 7.2 Hz, 1H), 5.04 (br. s, 1H), 4.88 (br. s, 1H), 4.45 (d, *J* = 3.4 Hz, 1H), 4.44- 4.39 (m, 1H), 3.97- 3.92 (m, 1H), 3.61 (dd, *J* = 9.9, 8.2), 3.44 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.20 (dd, *J* = 17.7, 7.2 Hz, 1H), 2.95 (dd, *J* = 17.1, 5.0 Hz, 1H), 2.40- 2.33 (m, 2H), 2.29- 2.25 (m, 1H), 2.13 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.05- 2.00 (m, 1H), 1.65- 1.60 (m, 1H), 1.43 (s, 3H), 1.37 (s, 12H), 1.06 (s, 9H), 0.90 (s, 9H), 0.75 (d, *J* = 6.9 Hz, 1H), 0.01 (s, 6H);

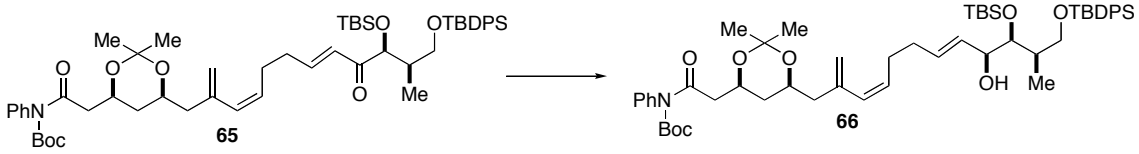
$^{13}$C NMR (125 MHz, $CDCl_3$) δ201.6, 173.0, 152.5, 146.5, 141.0, 138.8, 135.5 (2 signals), 133.7, 133.6, 130.8, 130.5, 129.6, 129.5, 128.9, 128.2, 127.7, 127.6 (2 signals), 126.0,

116.1, 98.7, 83.1, 77.4, 67.7, 66.0, 65.4, 44.6, 44.1, 40.4, 36.4, 32.9, 30.1, 29.6, 27.7, 27.1, 26.9, 25.8, 19.6, 19.2, 18.2, 10.4, -4.6, -5.2;

IR(film) 2930.5, 2857.2, 1737.6, 1707.7, 1624.1, 1471.9, 1369.7, 1293.8, 1256.2, 1155.2, 1089.6, 837.3, 777.4, 702.4 $cm^{-1}$;

Exact Mass Calc. for $C_{55}H_{79}NO_8Si_2$ $[M + Na]^+$ : 960.52364 ; found : 960.5101 (ESI)

***tert*-butyl (2-((4*S*,6*S*)-6-((3*Z*,7*E*,9*S*,10*S*,11*R*)-10-((*tert*-butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-9-hydroxy-11-methyl-2-methylenedodeca-3,7-dien-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetyl)(phenyl)carbamate**




Enone **65** (98.8 mg, 0.105 mmol, 1 eq) was dissolved in 2.5 mL THF and 1.0 mL MeOH was added under $N_2$. To the solution was added $CeCl_3 \bullet 7H_2O$ (0.168 mmol, 1.6 eq), which was allowed to dissolve, and the solution was cooled to -60 °C. The septum was briefly removed and 6 mg (0.158 mmol, 1.5 eq) $NaBH_4$ were added. TLC analysis is complicated by the fact that the product and starting material have the same $R_f$ and the reaction proceeds rapidly to overreduction upon warming in the spotter. After 30 minutes, the reaction was quenched by the addition of 0.1 mL acetone, immediately followed by 1 mL saturated $NH_4Cl_{(aq)}$. The reaction was diluted with 40 mL 90% EtOAc/hexanes and washed with brine, then dried over $Na_2SO_4$. Concentration *in vacuo* and purification of the residue by flash chromatography (10% EtOAc/hexanes), yielded 60.4 mg (0.0642 mmol, 61%) of allylic alcohol **66** as a clear colourless oil.

$R_f$ = 0.50 (20% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -0.9 (*c* 3.02, $CHCl_3$);

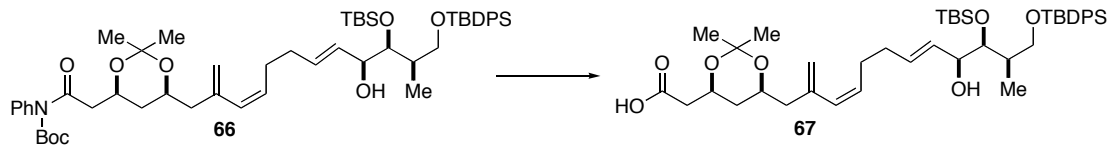
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.68- 7.63 (m, 4H), 7.45 – 7.41 (m, 2H), 7.40- 7.36 (m, 6H), 7.34- 7.31 (m, 1H), 7.10- 7.07 (m, 2H), 5.79 (ap. d, *J* = 11.7 Hz, 1H), 5.71 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.53- 5.44 (m, 2H), 5.03 (br. s, 1H), 4.92 (br. s, 1H), 4.45- 4.39 (m, 1H), 4.02- 3.97 (m, 1H), 3.97- 3.93 (m, 1H), 3.80- 3.77 (m, 1H), 3.61- 3.58 (m, 1H), 3.55- 3.51 (m, 1H), 3.20 (dd, *J* =17.3, 7.3 Hz, 1H), 2.96 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.55 (d, *J* = 4.7 Hz, 1H), 2.39 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.34- 2.30 (m, 1H), 2.17- 2.11 (m, 3H), 1.90- 1.84 (m, 1H), 1.64 (dt, *J* = 12.7, 2.2), 1.44 (s, 3H), 1.38 (s, 3H), 1.37 (s, 9H), 1.06 (s, 9H), 0.89 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 1H), 0.10 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.1, 152.6, 141.1, 138.9, 135.5, 133.7, 133.6, 132.3, 131.7, 130.9, 130.0, 129.6, 128.9, 128.2, 127.7, 127.6, 116.0, 98.7, 83.1, 75.6, 73.6, 67.7, 66.0, 65.9, 44.6, 44.2, 38.9, 36.4, 32.8, 30.1, 28.2, 27.8, 26.8, 26.0, 19.6, 19.2, 18.3, 11.3, -4.1, -4.4;

IR(film) 3541.2, 2930.4, 2856.5, 1737.4, 1707.8, 1471.9, 1369.9, 1293.5, 1256.0, 1154.8, 1111.6, 1089.0, 834.7, 776.0, 702.1;

Exact Mass Calc. for $C_{55}H_{81}NO_8Si_2$ $[M + Na]^+$ : 962.53929 ; found : 962.5288 (ESI)

**2-((4*S*,6*S*)-6-((3*Z*,7*E*,9*S*,10*S*,11*R*)-10-((*tert*-butyldimethylsilyl)oxy)-12-((*tert*-butyldiphenylsilyl)oxy)-9-hydroxy-11-methyl-2-methylenedodeca-3,7-dien-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid**




Amide **66** (60.4 mg, 0.0685 mmol, 1 eq,) was dissolved in 2 mL THF, cooled to 0 ºC , 0.2 mL of 30 % $H_2O_{2(aq)}$, 0.1 mL $LiOH_{(aq)}$ (1M). After 1h, TLC (50 % EtOAc/hexanes) showed complete consumption of the starting material. The reaction was quenched with saturated $Na_2SO_{3(aq)}$ until neutral to peroxide test paper, and then acidified with pH 2 buffer and extracted with 90% EtOAc/hexanes, washed with brine, and dried over $Na_2SO_4$. Solvent was removed *in vacuo* and the residue was purified by flash chromatography using 50% EtOAc/hexanes to afford 30.0 mg (0.0392 mmol, 57 %) of seco acid **67** as a clear colourless oil.

$[\alpha]^{20}_D$ = -22.1 (*c* 1.50, $CHCl_3$);

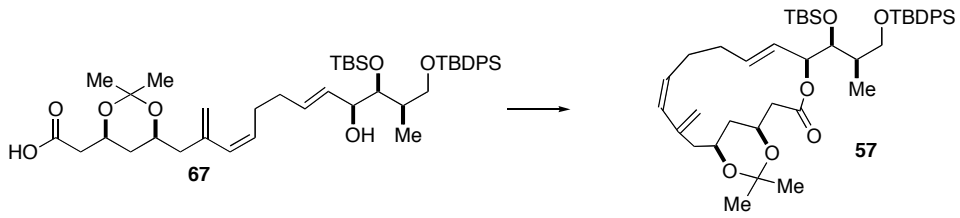
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.63 (m, 4H), 7.46- 7.41 (m, 2H), 7.41- 7.36 (m, 4H), 5.81- 5.74 (m, 2H), 5.55- 5.49 (m, 1H), 5.46 (dd, *J* = 15.4, 7.3 Hz, 1H), 5.07 (br. s, 1H), 4.92 (br. s, 1H), 4.24- 4.18 (m, 1H), 4.10- 4.07 (m, 1H), 3.92- 3.87 (m, 1H), 3.82- 3.79 (m, 1H), 3.57 (d, *J* = 6.6 Hz, 1H), 2.60 (dd, *J* = 14.8, 5.4 Hz, 1H), 2.48- 2.35 (m, 3H), 2.31- 2.23 (m, 1H), 2.20- 2.05 (m, 3H), 1.88- 1.82 (m, 1H), 1.62 (d, *J* = 13.0 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.14 (q, *J* = 12.6 Hz, 1H), 1.06 (s, 9H), 0.89 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.11 (s, 3H), 0.04 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.0, 140.8, 135.6, 133.6, 133.5, 132.9, 132.0, 130.1, 130.0, 129.6, 127.6, 116.5, 99.0, 75.5, 73.7, 67.6, 66.1, 65.7, 44.2, 41.3, 39.0, 35.9, 32.6, 30.0, 27.9, 26.9, 26.0, 19.7, 19.2, 18.3, 11.3, -4.1, -4.3;

IR(film) 3544.5, 2930.0, 2857.0, 1714.1, 1471.9, 1428.1, 1380.3, 1254.2, 1200.9, 1167.9, 111.8, 834.8, 776.8, 702.1 $cm^{-1}$;

Exact Mass Calc. for $C_{44}H_{68}O_7Si_2$ $[M + Na]^+$ : 787.4396 ; found : 787.4380 (ESI)

**(1*S*,5*S*,6*E*,10*Z*,14*S*)-5-((5*S*,6*R*)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-16,16-dimethyl-12-methylene-4,15,17-trioxabicyclo[12.3.1]octadeca-6,10-dien-3-one**




Seco acid **67** (30 mg, 0.0392 mmol) was dissolved in 5 mL $CH_2Cl_2$ and added over a period of 2 hours to a solution of 23.9 mg DMAP (0.196 mmol, 5 eq) and 33.7 mg MNBA (0.098 mmol, 2.5 eq) in 1 mL $CH_2Cl_2$ by syringe pump. After the addition was complete, the syringe was washed with a further 1 mL $CH_2Cl_2$. The reaction was concentrated after a further hour, and the residue was purified by flash chromatography (20 % EtOAc/hexanes) to afford 29.8 mg (quant) of macrocycle **57** as a clear colourless oil.

TLC $R_f$ = 0.75 (20 % EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = +14.9 (*c* 1.49, $CHCl_3$);

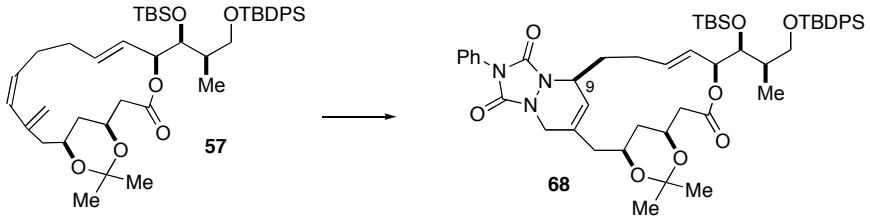
$^1$H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.63 (m, 4H), 7.46- 7.42 (m, 2H), 7.41 – 7.36 (m, 4H), 5.79 (d, *J* = 11.7 Hz, 1H), 5.72- 5.66 (m, 1H), 5.47- 5.38 (m, 2H), 5.15 (br. s, 1H), 5.13 (ap. t, *J* = 7.7 Hz, 1H), 4.97 (br. s, 1H), 4.25- 4.20 (m, 1H), 4.06 (dd, *J* = 8.8, 1.1, 1H), 3.91- 3.85 (m, 1H), 3.57 (t, *J* = 8.l), 3.39 (dd, *J* = 10.1, 6.2 Hz, 1H), 2.68- 2.61 (m, 2H), 2.41- 2.31 (m, 2H), 2.31- 2.26 (m, 1H), 2.15- 2.09 (m, 1H), 1.95 (ap. t, *J* = 11.3 Hz, 1H), 1.78- 1.71 (m, 1H), 1.49 (s, 3H), 1.41 (s, 3H), 1.08 (s, 9H), 0.81 (s, 9H), 0.72 (d, *J* = 6.9 Hz, 1H), 0.06 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.5, 140.0, 135.6 (broad signal), 133.6, 133.0, 132.1, 129.6 (2 signals), 127.6, 127.2, 117.5, 98.9, 76.5, 72.4, 70.1, 67.5, 66.0, 43.5, 42.5, 37.6, 35.4, 32.6, 30.1, 29.7, 28.3, 26.9, 25.8, 20.0, 19.2, 18.3, 9.3, -4.1, -4.4;

IR(film)2930.0, 2967.0, 1714.1, 1471.9, 1429.1, 1380.3, 1254.2, 1111.9, 834.8, 776.8, 702.1;

Exact Mass Calc. for $C_{44}H_{68}O_6Si_2$ $[M + Na]^+$ : 769.42901 ; found : 769.4251 (ESI)

**PTAD Adduct with Z Acetonide**



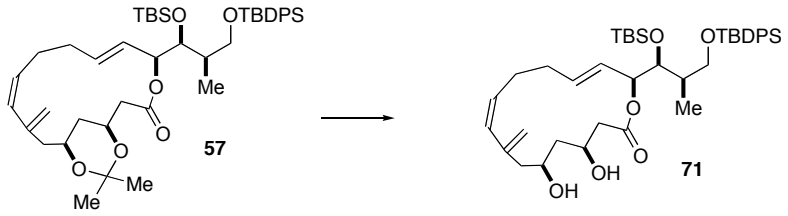

Macrocycle **57**, 2 mg, was dissolved in 1 mL $CDCl_3$ and a solution of 1 mg PTAD in $CDCl_3$ was added dropwise. As each drop was added, the colour persisted for several seconds. When the colour did not fade, the addition was stopped. Solvent was removed *in vacuo* and the residue was purified by flash chromatography (50 % EtOAc/hexanes) to give a clear colourless oil.

Partial Characterization data:

$^1$H NMR (600 MHz, $CDCl_3$) δ

Exact Mass Calc. for $C_{52}H_{71}N_3O_8Si_2$ $[M + Na]^+$ : 944.4672 ; found : 944.4648 (ESI)

**(4*S*,6*S*,9*Z*,13*E*,15*S*)-15-((5*S*,6*R*)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-4,6-dihydroxy-8-methyleneoxacyclopentadeca-9,13-dien-2-one**




Macrocycle **57** (15 mg, 0.0199 mmol, 1 eq) was dissolved in 2 mL of a 1: 1 mixture of $CH_2Cl_2$ and MeOH and cooled to 0 ºC. A crystal of CSA was added. After 1 hour, TLC (20% EtOAc/hexanes) shows complete consumption of starting material. The reaction was diluted with 20 mL EtOAc/hexanes, washed with $NaHCO_{3(aq)}$ and dried over $Na_2SO_4$. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (20% EtOAc/hexanes) to give 6.4 mg of **71** (0.0091 mmol, 45 %) as a clear colourless oil.

Partial Characterization Data:

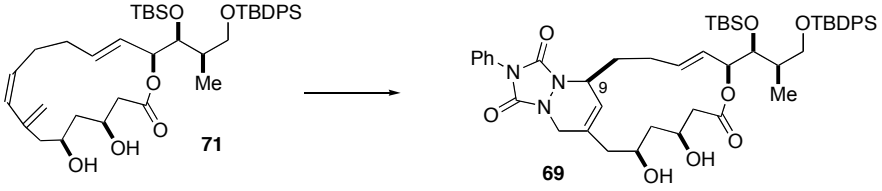
TLC $R_f$ = 0.15 (20 % EtOAc/hexanes, stains blue in CAM)

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.63 (m, 4H), 7.45- 7.42 (m, 2H), 7.41- 7.36 (m, 1H), 5.75- 5.69 (m, 2H), 5.46- 5.42 (m, 1H), 5.35 (dd, *J* = 15.4, 7.3 Hz, 1H), 5.14- 5.10 (m, 2H), 4.95 (m, 1H), 4.36- 4.31 (m, 1H), 4.05 (dd, *J* = 8.7. 1.3 Hz, 1H), 3.85- 3.80 (m, 1H), 3.58 (t , *J* = 10.0 Hz, 1H), 3.39 (dd, *J* = 10.1, 6.2 Hz), 3.07 (br. s, 1H), 2.68 (dd, *J* = 15.3, 2.9 Hz, 1H), 2.56 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.45 (dd, *J* = 15.4, 10.7 Hz, 1H), 2.41- 2.34 (m, 1H) 2.30- 2.23 (m, 1H), 2.16- 2.09 (m, 2H), 1.75- 1.69 (m, 1H), 1.56 (br. s, 1H), 1.52- 1.40 (m, 1H), 1.07 (s, 9 H), 0.83 (s, 9H), 0.71 (d, *J* = 6.7 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H);

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.8. 140.5, 135.6, 135.5, 134.8, 133.8 (2 signals), 133.6, 130.5, 129.6, 127.6, 126.9, 117.6, 72.1, 72.0, 69.2, 65.9, 46.8, 52.8, 42.1, 37.7, 32.5, 29.7, 28.7, 26.9, 25.9, 19.2, 18.2, 9.2, -4.0, -4.4;

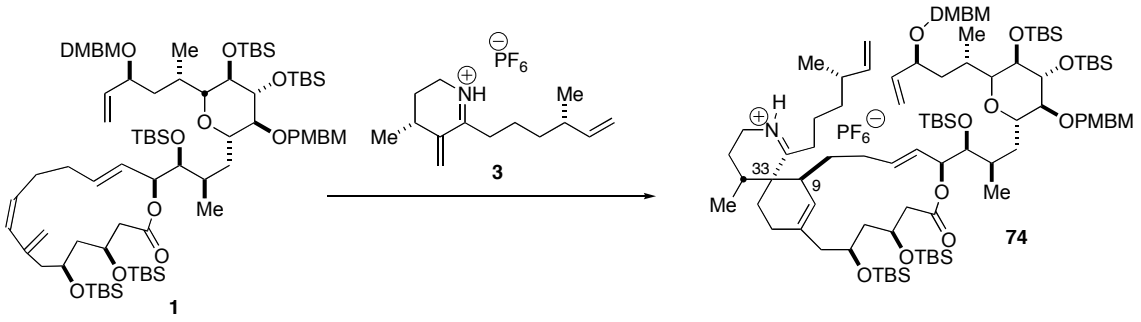
Exact Mass Calc. for $C_{41}H_{62}O_6Si_2$ $[M + Na]^+$ : 729.3977 ; found : 729.3977 (ESI)

**Major PTAD Adduct with Z Diol**




Diol **71** ( 1 mg) was mixed with 0.5 mg PTAD in 1 mL $CDCl_3$. After complete consumption of **71**, the residue was purified by flash chromatography (40 % EtOAc/hexanes) to give **69** as a clear colourless oil.

**Elaborate Diels Alder**




To 800 μL of 1,2 Dichloroethane, feshly passed through a column of 80- 200 mesh Aluminia, Basic Brockman activity 1, were added 10 μL 3- fluoropyridine (0.116 mmol). Seperately, *Z* macrocycle **1** (41 mg, 0.028 mmol, 1 eq) and iminium **3** (29 mg, 0.083 mmol, 3.0 eq) were mixed in 1 mL DCM in a 5 mL conical flask and the solvent was immediately removed *in vacuo*. The resulting tan foam was held under high vacuum with a stir bar for 15 minutes. Subsequently, the flask was backfilled with nitrogen and 200 μL of the 3-fluoropyridine solution (0.029 mmol, 1 eq) was added. The mixture was swirled to dissolve the foam and then was sealed and placed in a 40 °C oil bath. The reaction was stirred for 72 hours, after which time the solvent was removed *in vacuo*. Analysis by $^{1}H$ NMR indicated a roughly 1: 3 ratio of unconsumed Z macrocycle **1** to desired product. The ratio of desired product to undesired diastereomer was 9 : 1. The residue was redissolved in 20 mL $CH_2Cl_2$ and washed with 2x 5 mL 1.0 M $NaOH_{(aq)}$. Purification was accomplished by chromatography with 50 % EtOAc/hexanes. The first fractions contained 12.7 mg of recovered diene (0.0086 mmol, 31 %). All product containing fractions were concentrated and re-dissolved in 2 mL $CH_2Cl_2$. A drop of TFA was added and volatiles were removed *in vacuo*. The residue was taken up in 10 mL $CH_2Cl_2$ and washed 2x with saturated $NaPF_{6(aq)}$. Concentration *in vacuo* gave 25 mg (0.014 mmol, 49 %) of **74** as a tan foam

$R_f$ = 0.15 (50% EtOAc/hexanes, UV active, stains blue in CAM)

$[\alpha]^{20}_D$ = -33.0 (*c* 0.735, $CHCl_3$);

$^1$H NMR (600 MHz, $CDCl_3$) δ 10.76 (br. s, 1H), 7.24 (ap. d, *J* = 8.5 Hz, 2H), 6.89- 6.86 (m, 4H), 6.64- 6.61 (m, 1H), 5.73 (ddd, *J* = 17.4, 10.2, 7.9 Hz, 1H), 5.66 (ddd, *J* = 17.9, 10.3, 7.8 Hz, 1H), 5.41 (td, *J* = 14.5, 2.5 Hz, 1H), 5.26 (br. s, 1H), 5.24- 5.21 (m, 1H), 5.06- 5.03 (m, 1H), 5.00 (ap. d, *J* = 17.4 Hz, 1H), 4.93 (ap. d, *J* = 10.2 Hz, 1H), 4.84- 4.79 (m, 3H), 4.68- 4.64 (m, 2H), 4.61 (d, *J* = 17.0 Hz, 1H), 4.59 (d, *J* = 17.3 Hz, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.23- 4.19 (m, 1H), 4.00- 3.93 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.76 (d, *J* = 8.2 Hz, 1H), 3.73- 3.70 (m, 1H), 3.63- 3.59 (m, 1H), 3.53- 3.48 (m, 1H), 3.42- 3.39 (m, 1H), 3.22- 3.19 (m, 1H), 2.95- 2.88 (m, 1H), 2.88- 2.82 (m, 2H), 2.46- 2.41 (m, 1H), 2.40- 2.31 (m, 3H), 2.22- 2.14 (m, 3H), 2.13- 2.03 (m, 4H), 1.97- 1.91 (m, 1H), 1.84- 1.77 (m, 2H), 1.77- 1.68 (m, 4H), 1.65- 1.56 (m, 2H), 1.49- 1.42 (m, 4H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92- 0.91 (m, 12H), 0.90 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.12- 0.09 (m, 21H), 0.09 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H);

$^1$H NMR (600 MHz, $C_6D_6$) δ 11.5 (br. s, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.03- 7.00 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 1H), 5.87- 5.79 (m, 2H), 5.68- 5.59 (m, 1H), 5.31- 5.18 (m, 4H), 5.16- 5.08 (m, 3H), 5.02 (d, *J* = 6.7 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.86- 4.82 (m, 2H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 8.5 Hz, 1H), 4.60 (d, *J* = 8.4 Hz, 1H), 4.49- 4.45 (m, 1H), 4.05 (ap. d, *J* = 8.2 Hz, 1H), 4.96- 4.93 (m, 1H), 4.92- 3.89 (m, 1H), 3.84- 3.78 (m, 2H), 3.70- 3.67 (m, 1H), 3.53- 3.49 (m, 1H), 3.51 (s, 3H), 3.45 (s, 3H), 3.33 (s, 3H), 3.00- 2.95 (m, 2H), 2.87- 2.80 (m, 1H), 2.67- 2.63 (m, 1H), 2.56 (dd, *J* = 9.2, 3.7 Hz, 1H), 2.53- 2.48 (m, 1H), 2.45- 2.38 (m, 2H), 2.30- 2.25 (m, 1H), 2.24- 2.19 (m, 1H), 2.17- 2.12 (m, 2H), 2.06- 1.96 (m, 4H),

1.94- 1.86 (m, 3H), 1.81- 1.74 (m, 2H), 1.71- 1.68 (m, 1H), 1.67- 1.61 (m, 1H), 1.61- 1.55 (m, 2H), 1.27 (d, $J$ = 6.6 Hz, 3H), 1.14 (d, $J$ = 7.7 Hz, 3H), 1.10- 1.07 (m, 12H), 1.05 (s, 9H), 1.02 (s, 9H), 1.00 (s, 9H), 1.00 (s, 9H), 0.69 (d, $J$ = 6.9 Hz, 3H), 0.28 (s, 3H), 0.27 (s, 6H), 0.26 (s, 3H), 0.25 (s, 3H), 0.20 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.18 (s, 6H);

$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 198.7, 170.5, 159.2, 149.0, 148.6, 143.6, 139.1, 135.0, 133.9, 130.5, 129.9, 129.2, 127.9, 122.6, 120.4, 117.3, 113.8, 113.4, 111.2, 111.0, 93.7, 91.6, 84.7, 81.9, 80.3, 77.1, 76.9, 75.6, 75.5, 75.0, 73.1, 72.8, 73.1, 72.8, 69.6, 69.2, 68.7, 66.8, 55.9, 55.8, 55.1, 47.4, 47.3, 46.3, 45.4, 42.9, 41.0, 39.0, 38.7, 37.1, 35.9, 33.5, 31.8, 30.9, 30.8, 29.7, 29.3, 28.8, 28.5, 28.3, 26.3, 26.1, 26.0, 25.9, 25.8 (2 signals), 24.5, 24.1, 22.7, 19.9, 18.5, 18.0 (3 signals), 17.9, 17.1, 13.6, 13.4, -3.2, 3.9 (3 signals), -4.0 (2 signals), -4,5 (2 signals);

IR(film) 3338.9, 3281.0, 2929.9, 2856.5, 1720.1, 1671.4, 1612.5, 1515.3, 1463.3, 1380.2, 1251.0, 1096.4, 1032.8, 838.2, 775.0;

Exact Mass Calc. for $C_{93}H_{164}NO_{15}Si_5^+$ $[M]^+$ : 1675.0941; found : 1675.0897 (ESI)

# *Appendix A*

## Proposal for a Bioinspired Synthesis of Spiro-Prorocentrimine

Inherent in the design of the intramolecular Diels- Alder substrate was the idea that the Diels–Alder event is a feasible macrocyclizing reaction. No studies on the biogenesis of the spiro-iminium natural products has been done with the exception of a feeding study preformed on the spirolide producing organism *Alexandrium ostenfeldii* conducted at the Institute for Marine Biosciences, National Research Council in Halifax, Nova Scotia.[1] In this work, feeding studies with [1,2- $^{13}C_2$]acetate, [1-$^{13}$C]acetate and [$^{15}$N]glycine showed a glycine origin for the terminal nitrogen, and incorporation of acetate for some but not all of the carbon backbone. Gene sequencing efforts of any polyketide synthetase relevant to the spiro-imines has been elusive.[2] However, it seems reasonable that an Diels–Alder reaction may be operative in the formation of all of the members of the spiro-iminium family of natural products.

With the assumption that nature produced spiro-prorocentrimine via a Diels–Alder reaction, a logical assumption is that iminium formation and ion separation[3] may provide means of enhancing the reactivity of the dienophile in the Diels–Alder reaction. In the absence of biosynthetic evidence from the organism that produces spiro-prorocentrimine, this can only be speculative, but there are no compelling reasons to doubt this hypothesis.

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(1) McKinnon, S. L.; Cembella, A. D.; Burton, I. W.; Lewis, N.; LeBlanc, P.; Walter, J. A. *J. Org. Chem.* **2006**, *71*, 8724- 8731.

(2) Yang, I.; John, E.; Beszteri, S.; Glöckner, G.; Krock, B.; Goesmann, A.; Cembella, A. D. *BMC Genomics*. **2010**, *11*, 248. Open access link: http://www.biomedcentral.com/1471-2164/11/248.

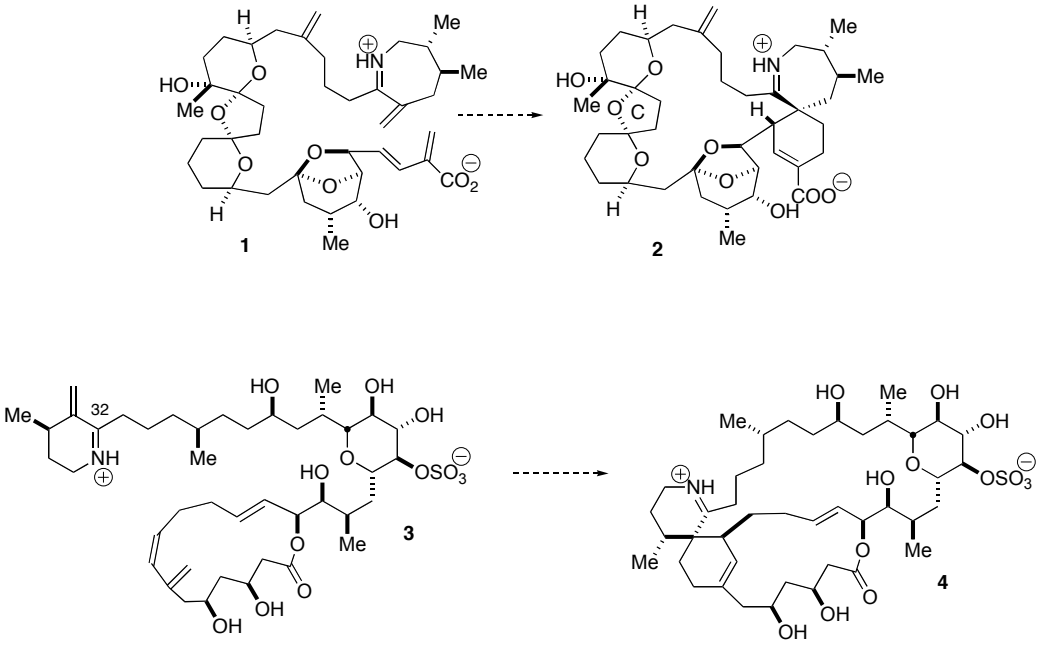



**Figure A.1** Iminium ion based biosynthetic hypothesis for **2** and **4**

A compound such as **1** could give rise to pinnatoxins **2**, while a compound such as **3** could give rise to spiro-prorocentrimine **4** (Figure A.1).

The failure of the intramolecular Diels- Alder in the Pero-Juhl route may be attributable to the fact that the reaction was attempted on a fully protected substrate. The transannular interactions between the bulky protecting groups may disrupt the desired Diels- Alder reaction. It certainly can be anticipated that removing protecting groups from the molecule would alleviate steric interactions in the approach of the diene and the dienophile. However, another possibility arises, that the removal of the protecting groups will actually result in attractive transannular interactions through the process of metal ion templating by coordination to the abundant oxygen atoms in **1** and **3**. The ion concentration of various cations within the cytoplasm of marine algae is kept relatively isotonic with seawater. Many of the intermolecular Diels–Alder reactions conducted in the course of this work were conducted at a concentration lower than that of several ions in sea water. For example, the concentration of $Na^+$ in seawater is 0.47 M, and the

concentration of $Mg^{2+}$ is 0.05 M.[4] Accordingly, it is possible that a Diels–Alder reaction to form spiro-prorocentrimine could be aided by the complexation of ions to a zwitterionic intermediate that lacks the 23 membered ring. Pinnatoxin also looks suited for such a templation. A possible arrangement is shown for pinnatoxin and spiro-prorocentrimine is shown in Figure A.2.

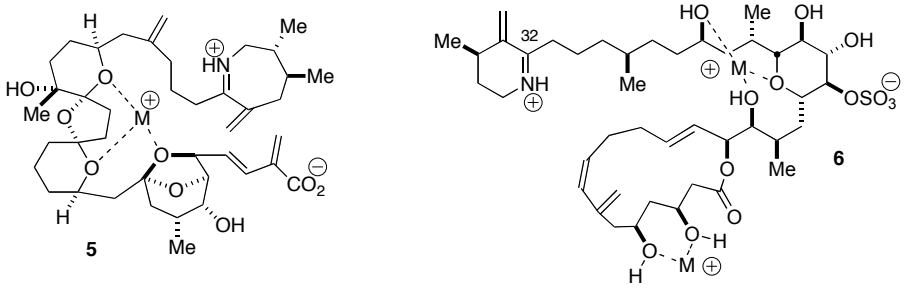


**Figure A.2** Metal ion templated Diels–Alder precursors

Such complexes could potentially bring the diene and dienophile parts much closer in space, promoting the reaction. A strategy to test this hypothesis could readily be based on the a synthesis of **3** employing chemistry described earlier in this thesis. Specifically, the diene containing fragment **7** (or its geometric isomer), enal **8**, central linker **9** and pyran enal **10** could all be conserved.[5]

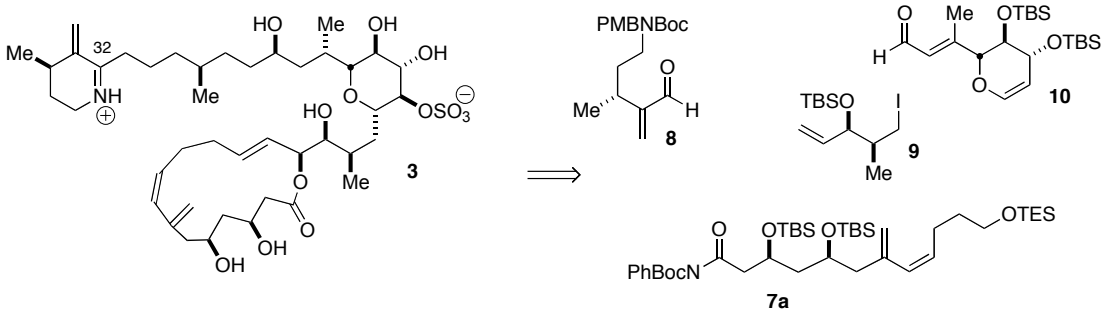


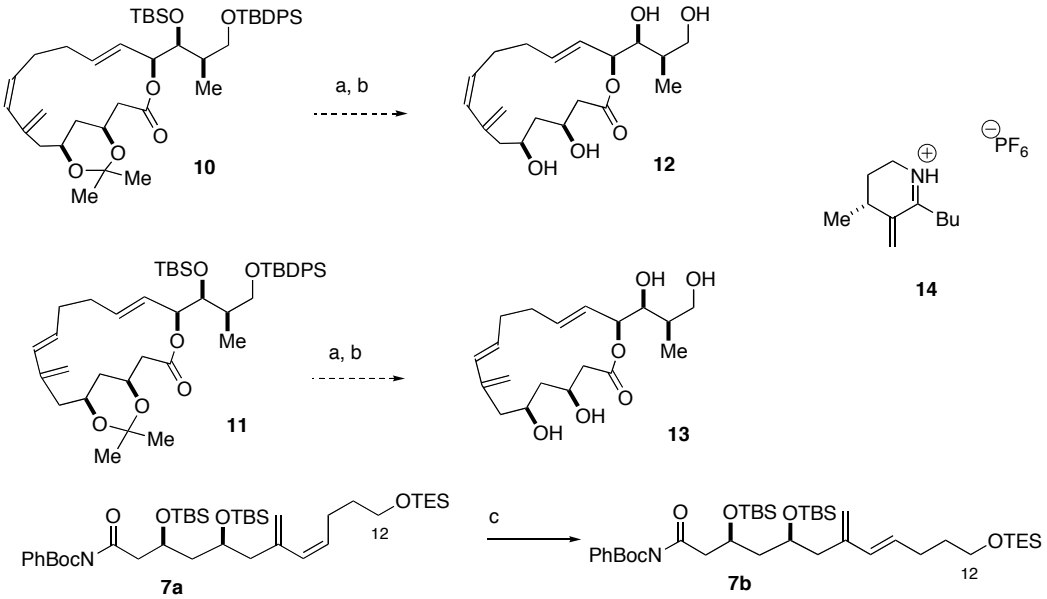
**Figure A.3** Components that may be conserved in the synthesis of **3**.

(4) Krumgalz, B. S.; Holzer, R. *Limnol. Oceanogr.* **1980**, *15*, 367- 370.

(5) Based on the robustness of Pinnatoxin A, as shown by Kishi, and the fragility of many of the spiro-prorocentrimine intermediates shown in the previous chapter, it may be worth considering testing the templating theory in a synthesis of Pinnatoxin rather than spiro-prorocentrimine.

Since the results from the previous chapter showed that a macrolactone ring contraction occurs during the deprotection of certain intermediates, and that the *Z* macrocycle is not readily isomerized to the *E* macrocycle with an acetonide or free hydroxyls at $C_3$ and $C_5$, the first order of business is to determine if the macrolactonization can be suppressed, and if the macrocycles with free hydroxyls do react with iminiums. Accordingly, known Z acetonide diene **10** would be remade, and *E* acetonide diene **11** would be prepared from an acyclic *E* diene. I recently observed that compound **7a** is cleanly and quantitatively isomerized to *E* diene **7b** by 1 mol% $I_2$ in $CDCl_3$.[6] This would simplify the contruction of *E* diene macrocycles. It is also possible $I_2$ could directly isomerize the macrocycles. These macrocycles would be treated with an anionic fluoride source to remove the silyl groups, while preserving the acetonides, then mild acid to attempt to remove the acetonides without rearrangement. If macrocycles **12** and **13** could be prepared, their reactivity and facial selectivity with dienophile **14** would be assessed (Scheme A.1)

**Scheme A.1**




(6) The protecting group at $C_{12}$ appears to be necessary for this clean transformation: Dr. Pero tried the same isomerization with a free OH at $C_{12}$ and complete decomposition, potentially through iodoetherification followed by HI production was observed.

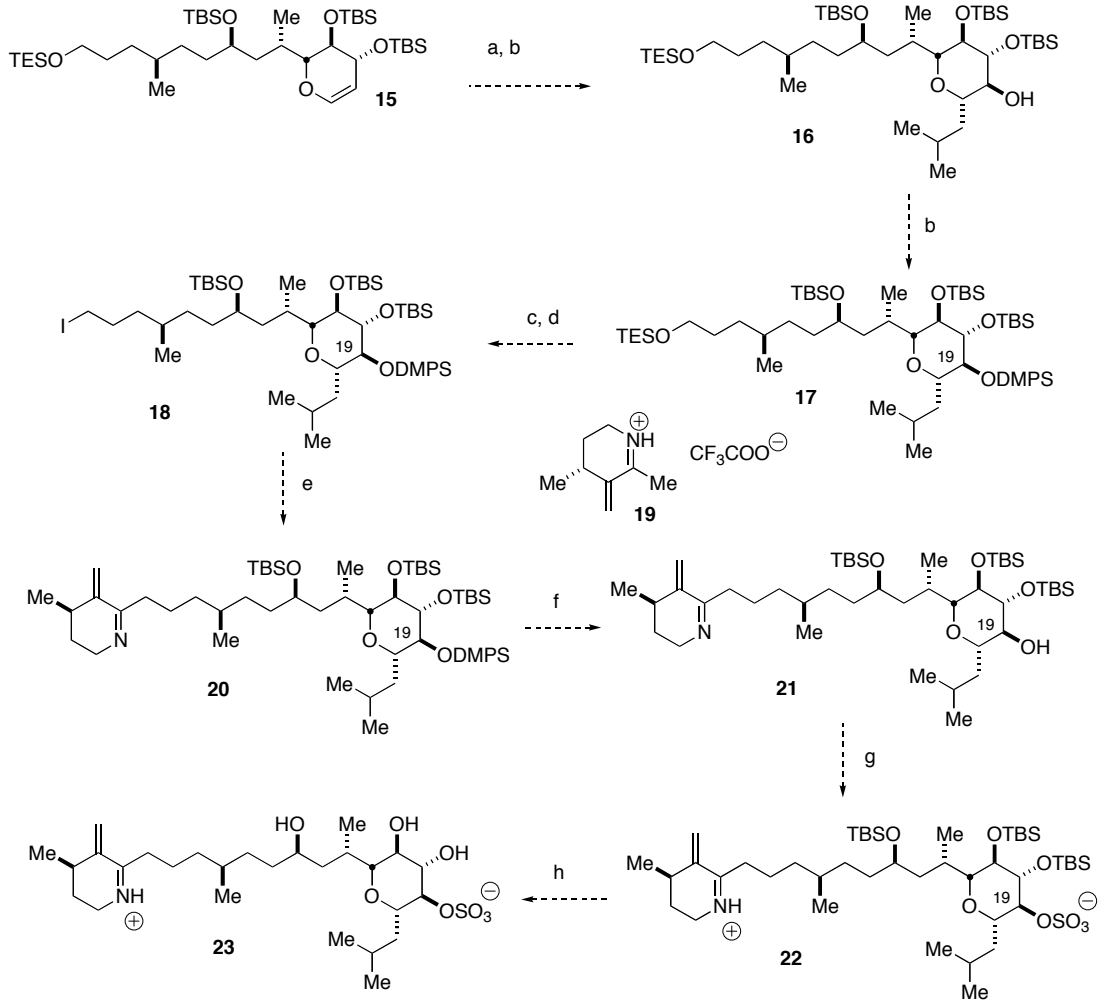
In the course of my studies, I made several observations that will affect the order of introduction of functional groups and choice of protecting groups. Since the synthesis of **3** requires installation of the sulfate before the Diels–Alder, the protecting group must be compatible with the diene. The *Z* diene is rapidly destroyed by DDQ. A silyl protecting group more labile than fluoride may be useful for sulfate installation before the global deprotection. Compound **14** is stable in the presence of both HF•py or TBAF in THF. The following strategy to test installation of the sulfate is proposed:

Glycal **15** would be epoxidized and opened by a simple Grignard to give alcohol **16** (Scheme A.2). This is protected by a candidate protecting group such as dimethylphenylsilyl to give compound **17**. The terminal protective group is then cleaved and and alkyl iodide **18** is prepared. An alkylation with a metalloenamine derived from **19**,[7] readily prepared from compound **8** is added to effect alkylation to give compound **20**. Finally deprotection of the group at $C_{19}$ and sulfation by exposure to $SO_3$•py would give zwitterion **21**.[8] Deprotection conditions would be screened to give compound **22**. If the alkylation did not work, the NHK reaction employed by Dr. Borg in chapter 3 could be used, however the preparation of the alkenyl iodide employed would have to be improved.

(7) Dr. Bindschädler showed that Metalloenamines may be prepared from compound **14** and acylated on N to form diene-carbamates with high yield. It is hoped the iodide would enable C-alkylation.

(8) Preliminary attempts I made to sulfate deprotected Diels–Alder adducts with $SO_3$•py gave species I believed to be zwitterionic, based on a decrease in polarity and on the absence of fluorinated anions by $^{19}F$ NMR and signals corresponding to pyridinium cations in $^{1}H$ NMR.

**Scheme A.2**

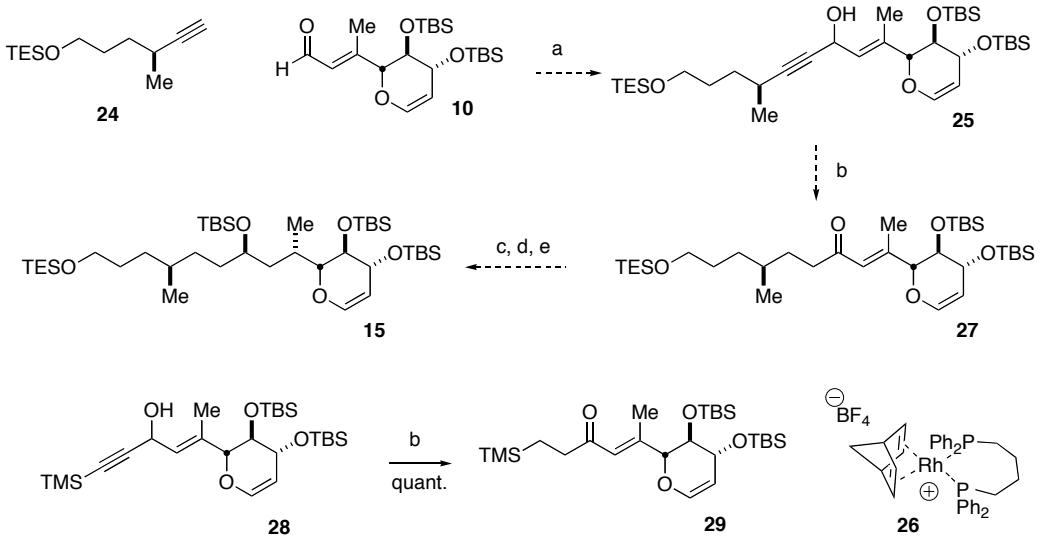



a) DMDO, $CH_2Cl_2$; b) *i*-BuMgCl, $Li_2CuCl_4$, THF; c) HF•py, $CH_3CN$; d) $PPh_3I_2$, im, $CH_2Cl_2$; e) MHMDS, **19**, then **18;** f) fluoride source (TAS-F); g) $SO_3$•$NMe_3$, DMF; h) Fluoride source, (TAS-F)

A tin free synthesis of compound **15** is proposed, starting from compound **10**. Addition of the anion of **24** to **10** would produce a inconsequential mixture of allylic alcohols **25**. Hydrogenation of this mixture with Brown catalyst **26** should yield enone **27**. Elaboration with known conditions should yield **15**. The hydrogenative coupling is predicated on an observation I made in which compound **28** was hydrogenated to enone **29** by Brown catalyst. Such rearrangements are known. [9]

(9) Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 2687- 2699.

**Scheme A.3**

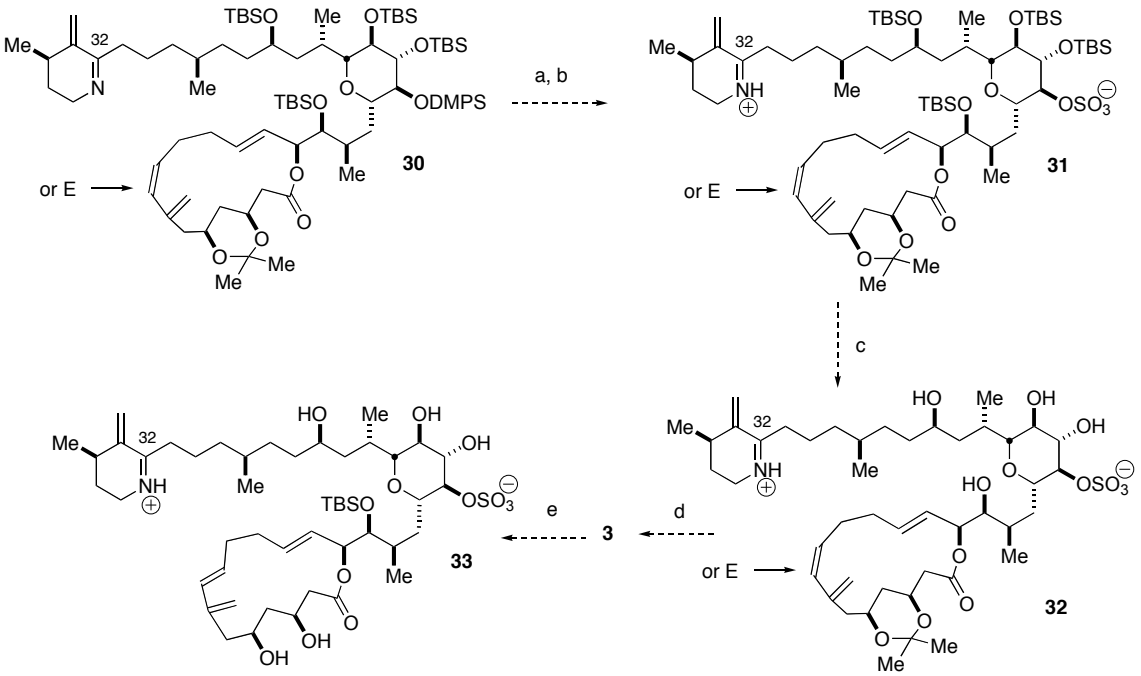



a) **24**, *n*-BuLi, then **10**, THF; b) **26**, 1 atm $H_2$, $CH_2Cl_2$; c) CBS, HBCat; d) Me(R,R)DuPhosRhCODBF$_4$, $H_2$, $CH_2Cl_2$
e) TBSOTf, 2,6 lutidine, $CH_2Cl_2$.

Subsequently, the chemistry described in Scheme A.2 would be applied to the real system to make compound **30**. Deprotection and sulfation to make **31** would be followed by global silyl removal to give **32**. Finally acetonide removal would give either Z compound **3**, or E compound **33**. At this point, the behaviour of the compound in the presence and asbsence of metal ions would be observed (Scheme A.4).

This strategy is attractive, as it represents a synthesis of spiro-prorocentrimine that could potentially be as few as **23** linear steps from tri-O-acetal-D-glycal. This would also enable the testing of the hypothesis that a metal ion template could facilitate an intramolecular Diels–Alder reaction in the synthesis of the spiro-imine toxins.

## Scheme A.4

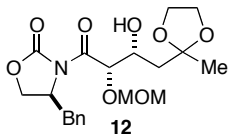



a) TAS-F; b) $SO_3 \bullet NMe_3$ c) TAS-F; d) CSA; e) $I_2$

# *Appendix B*

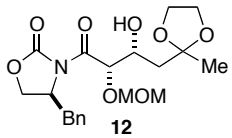
## NMR Spectra

# I. NMR Spectra From Chapter 2




**12**

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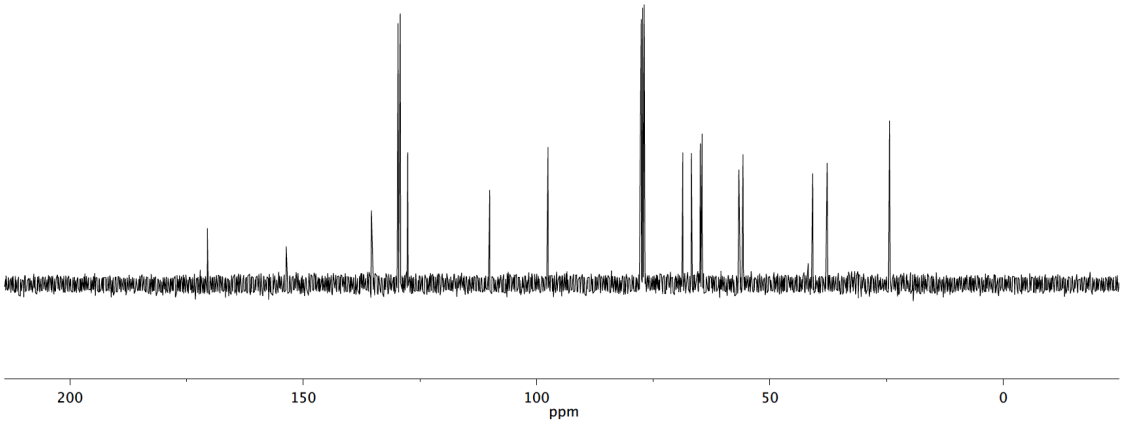

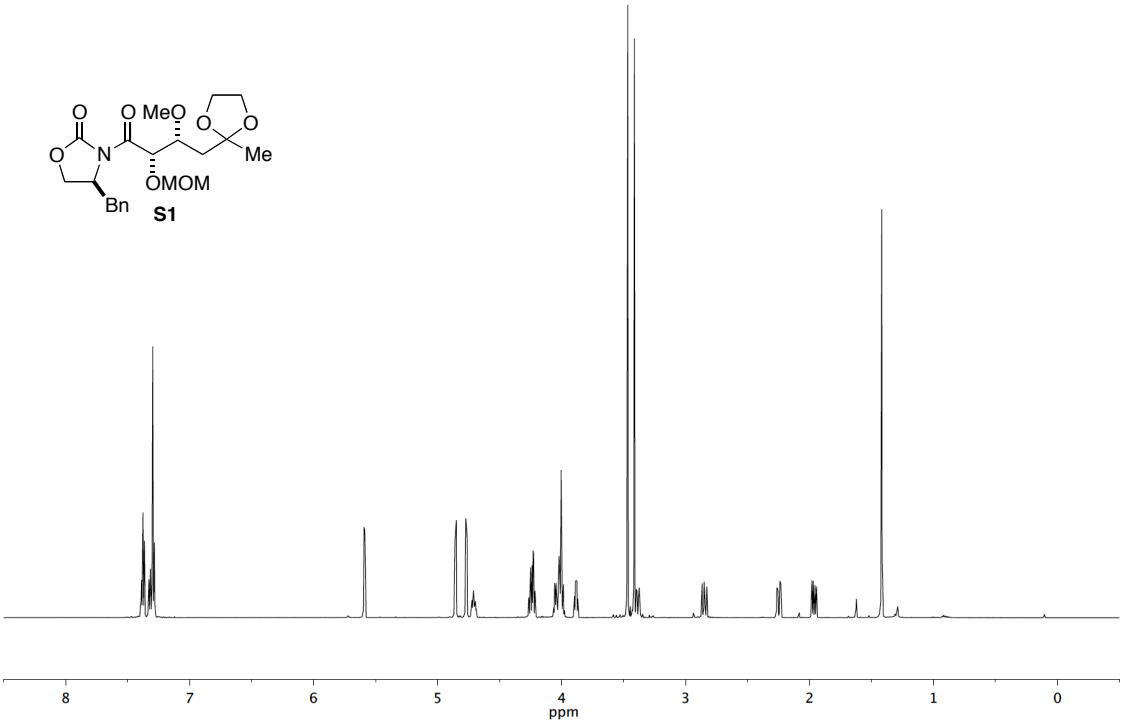
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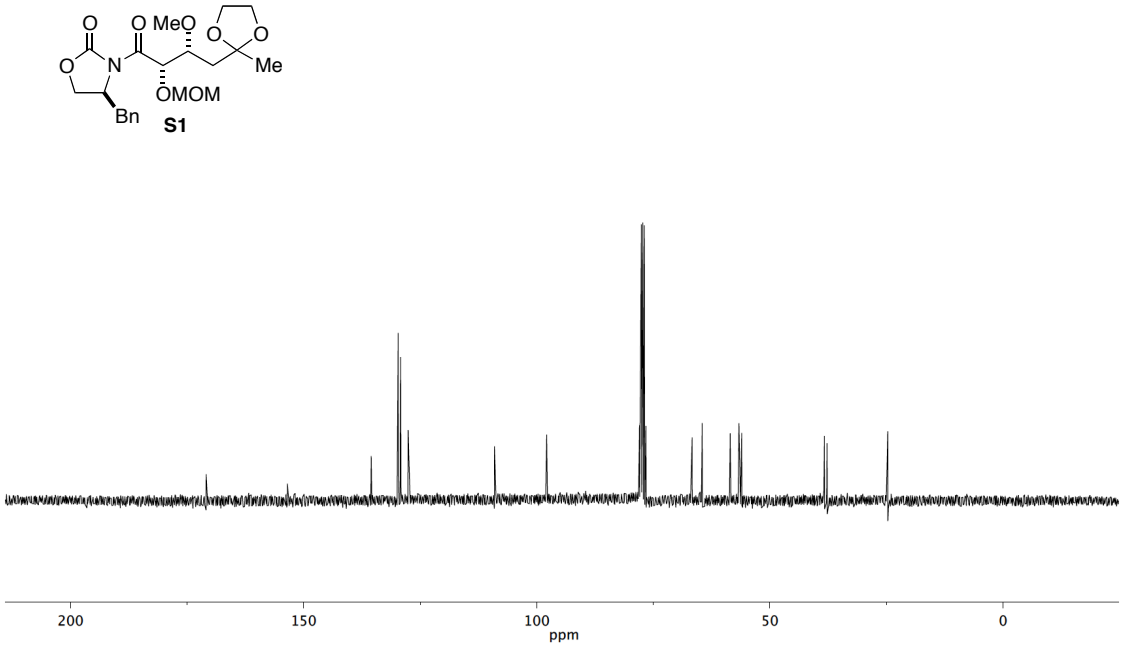
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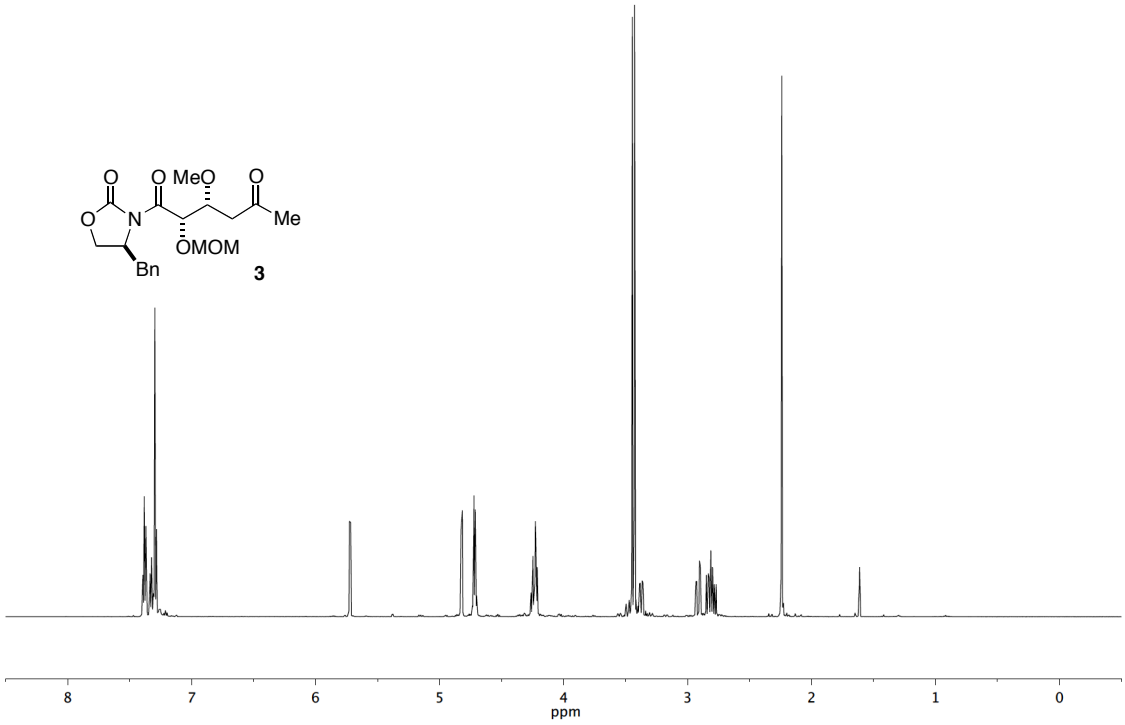
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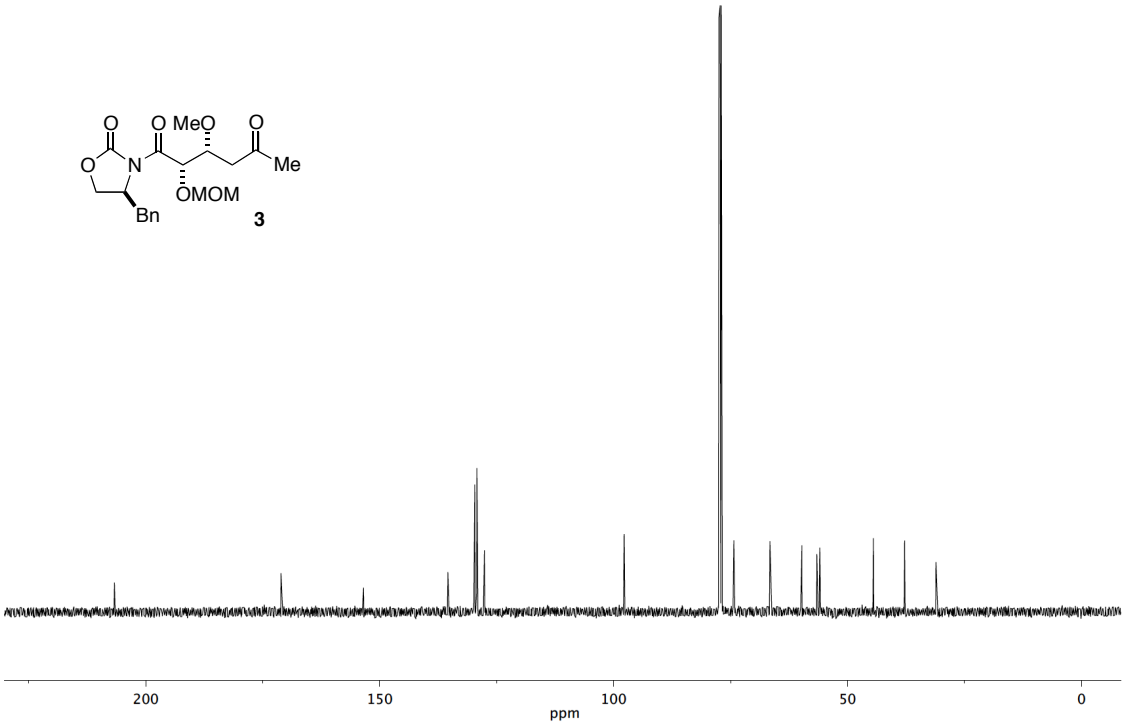
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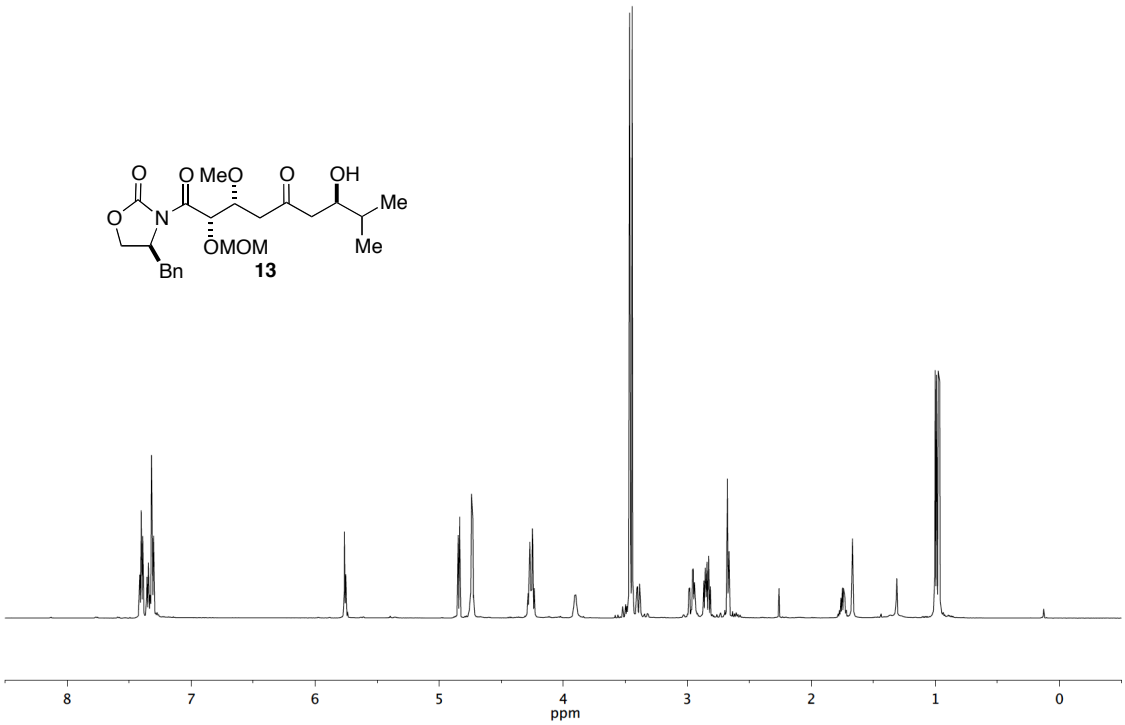
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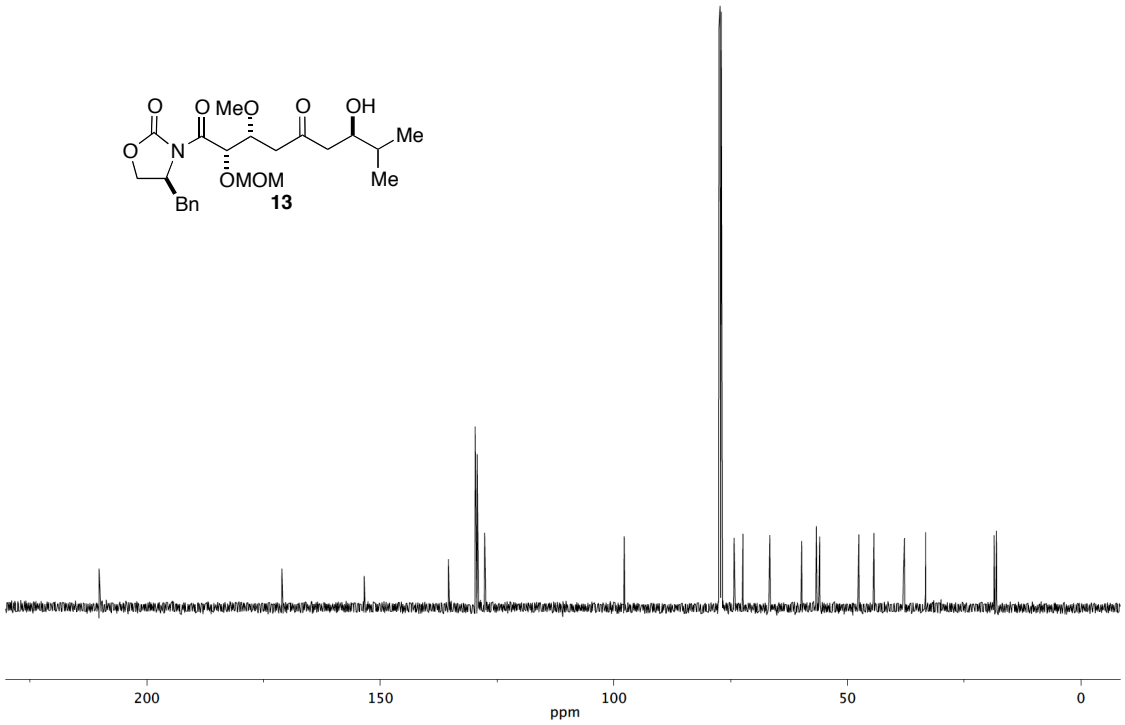
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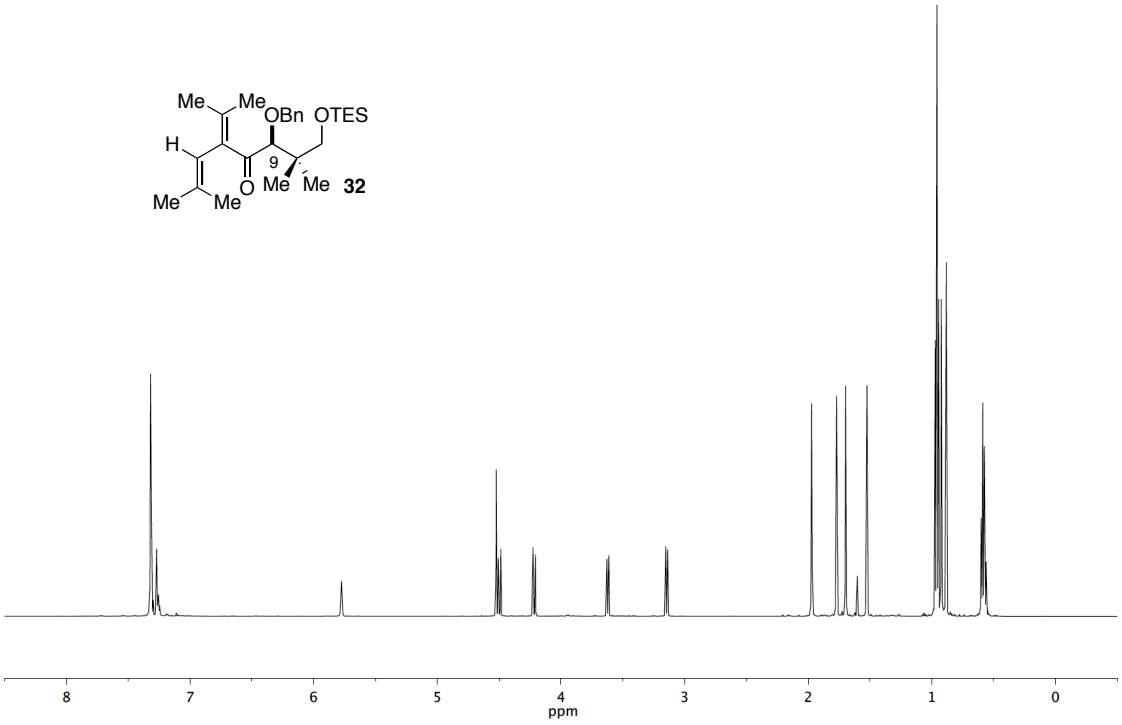
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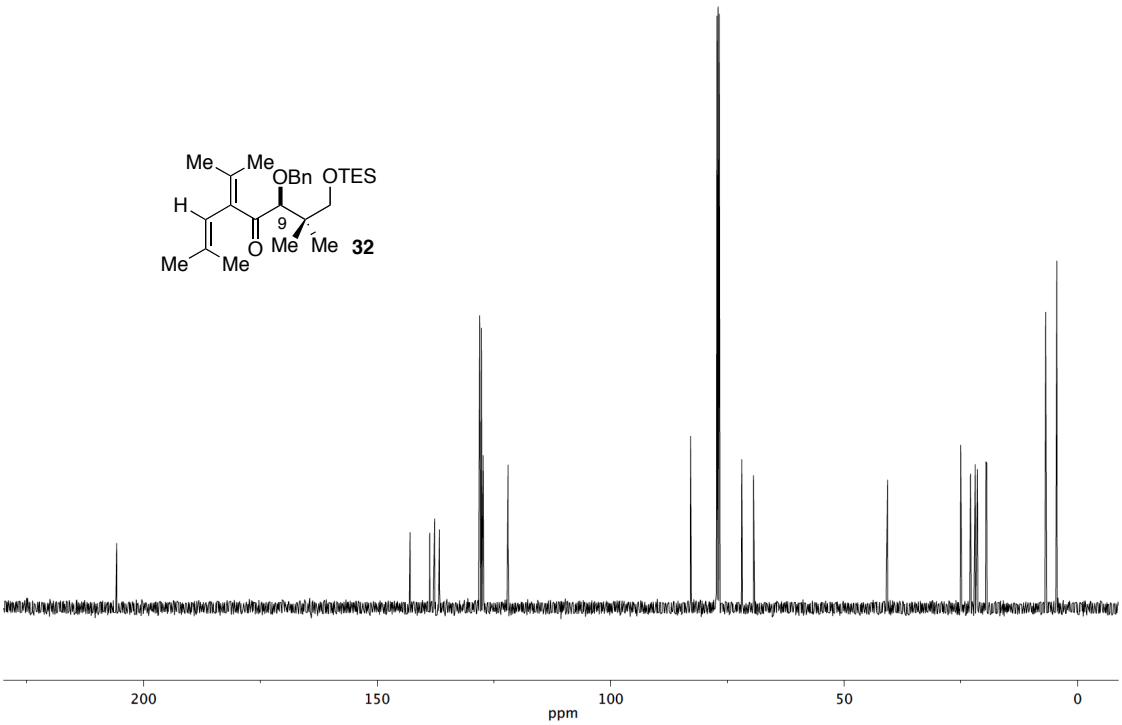
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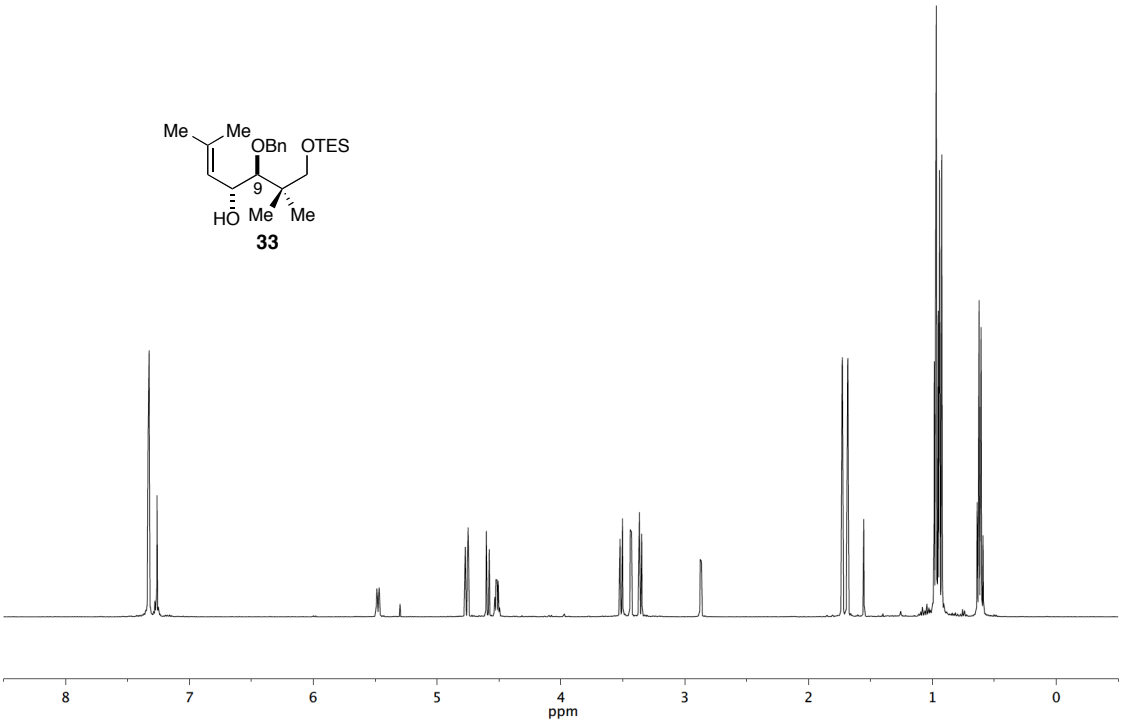
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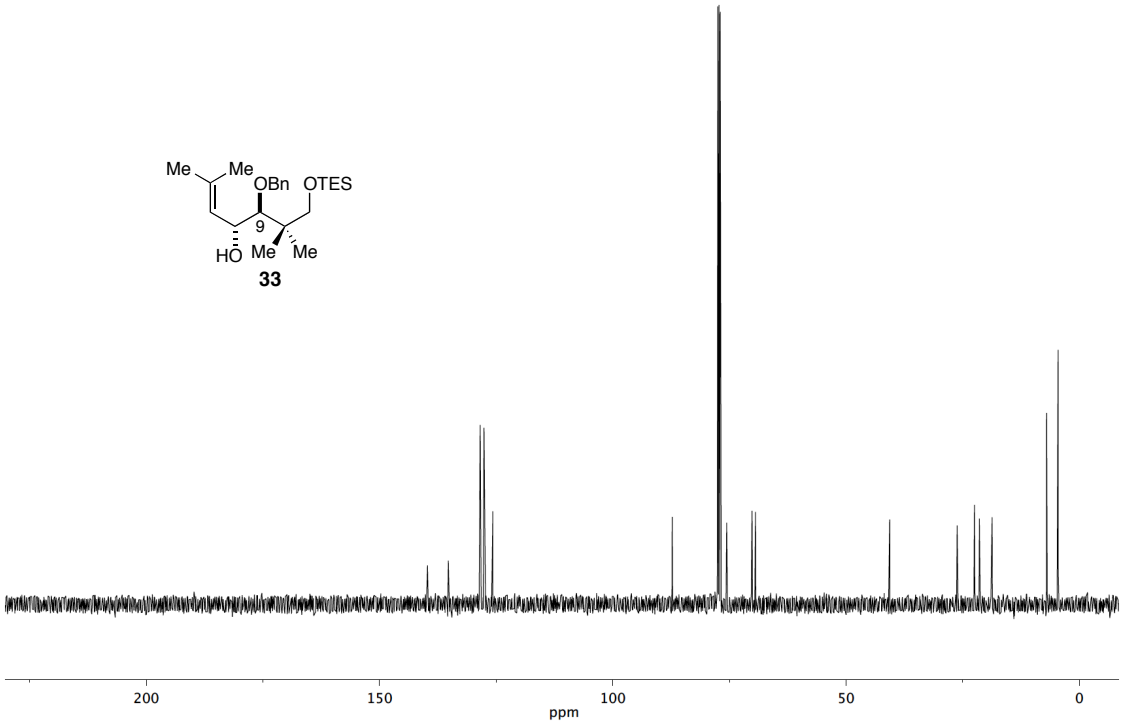
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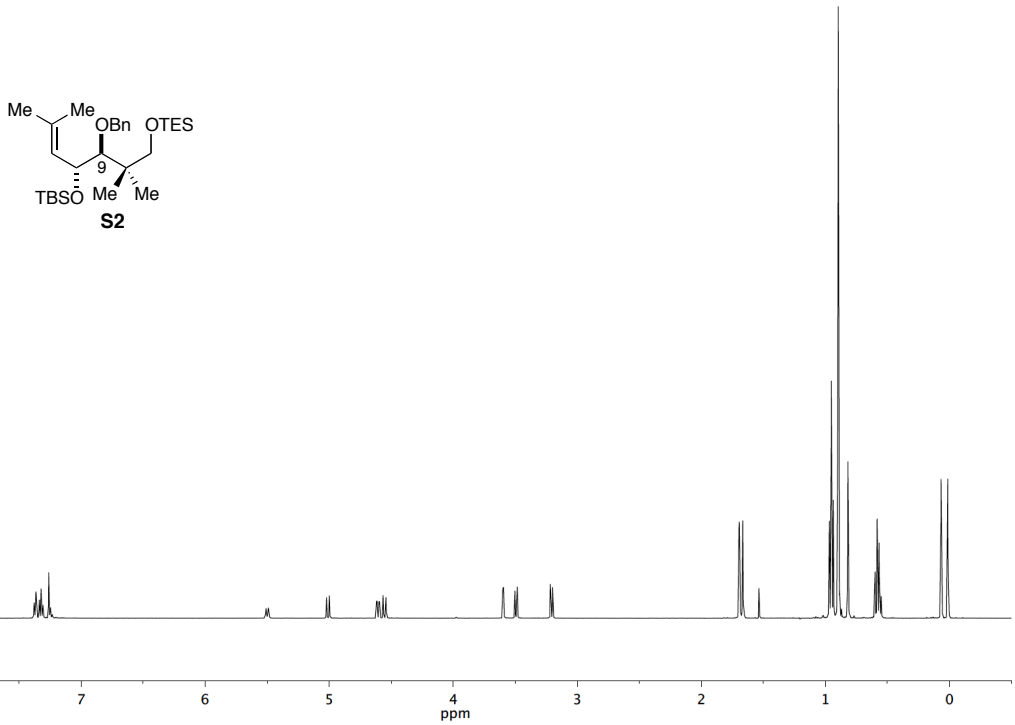
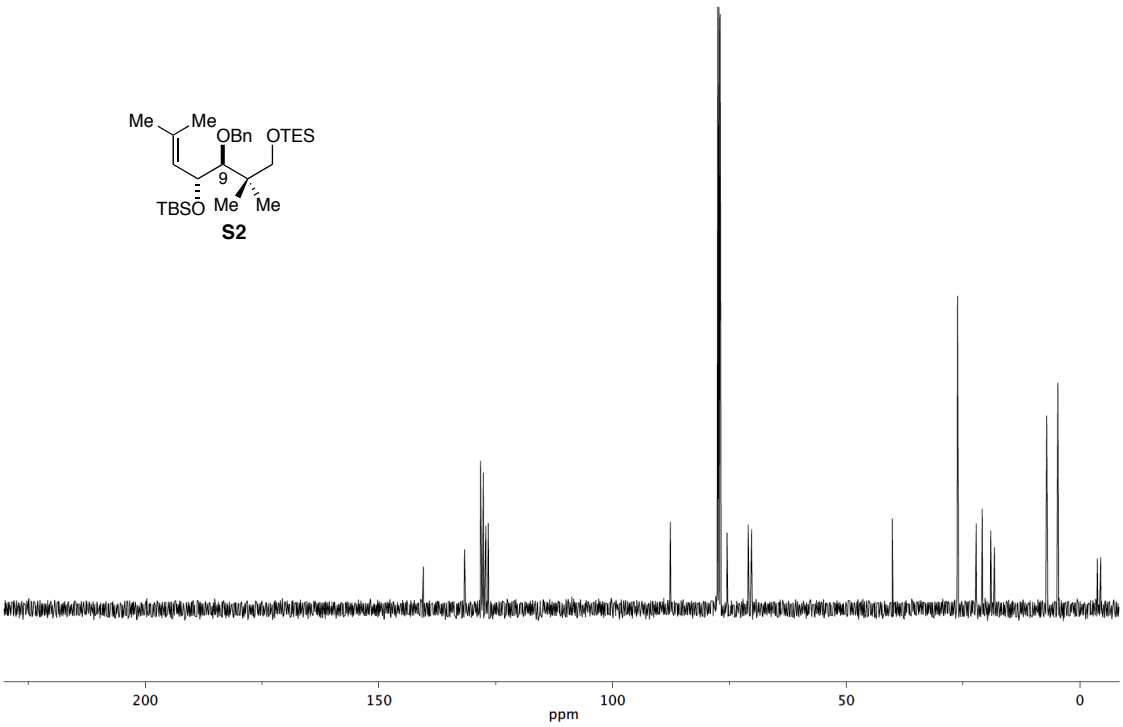
ppm

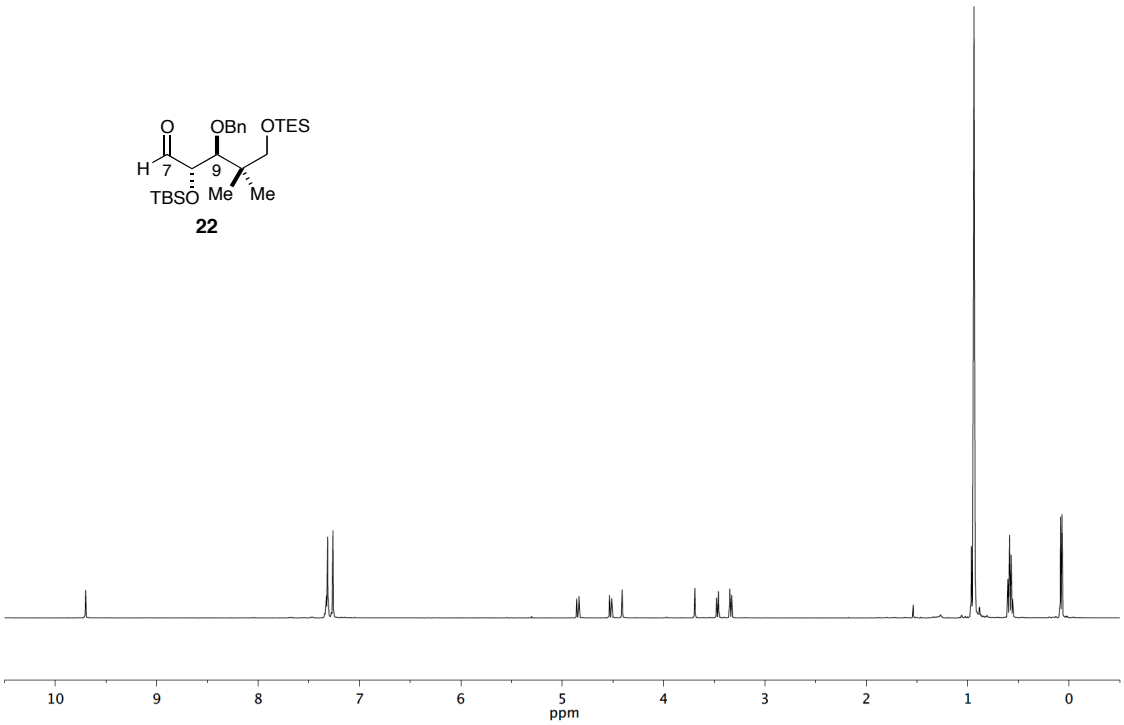
**33**

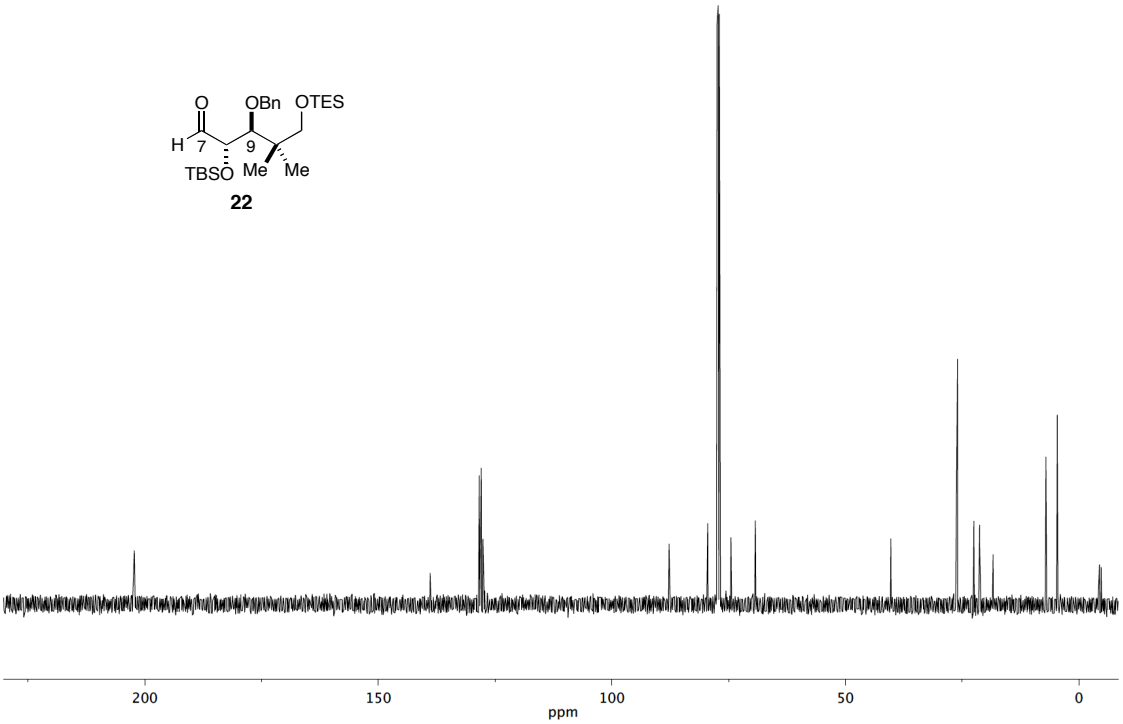

Me
Me
OBn
OTES
9
TBSO
Me
Me
8
7
6
5
4
3
2
1
0
ppm

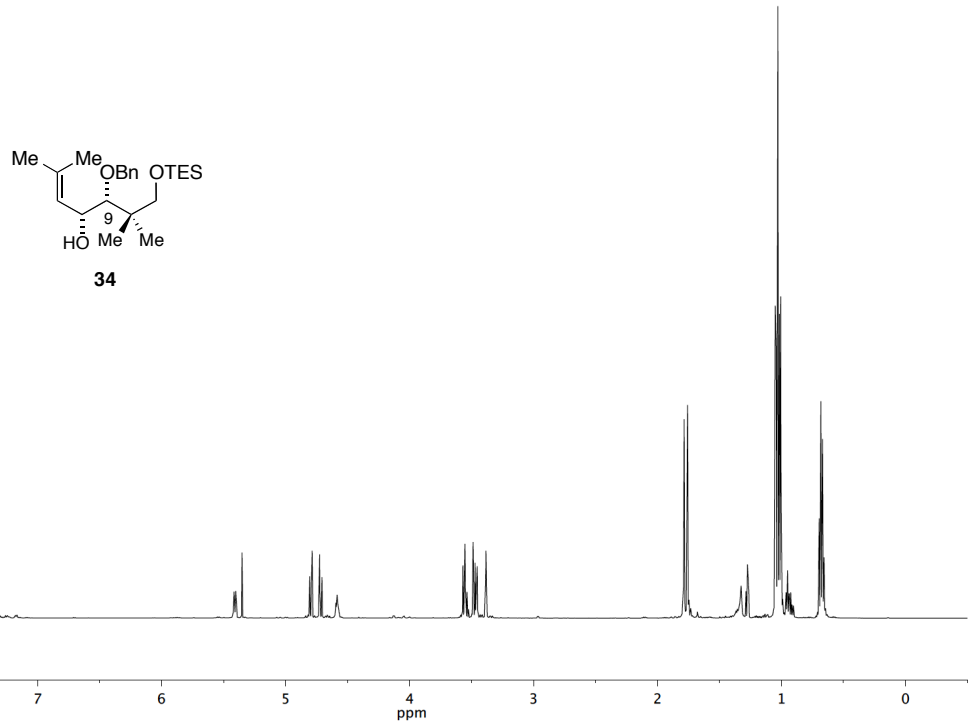
**S2**


Me
Me
OBn
OTES
9
TBSO
Me
Me
200
150
100
50
0
ppm

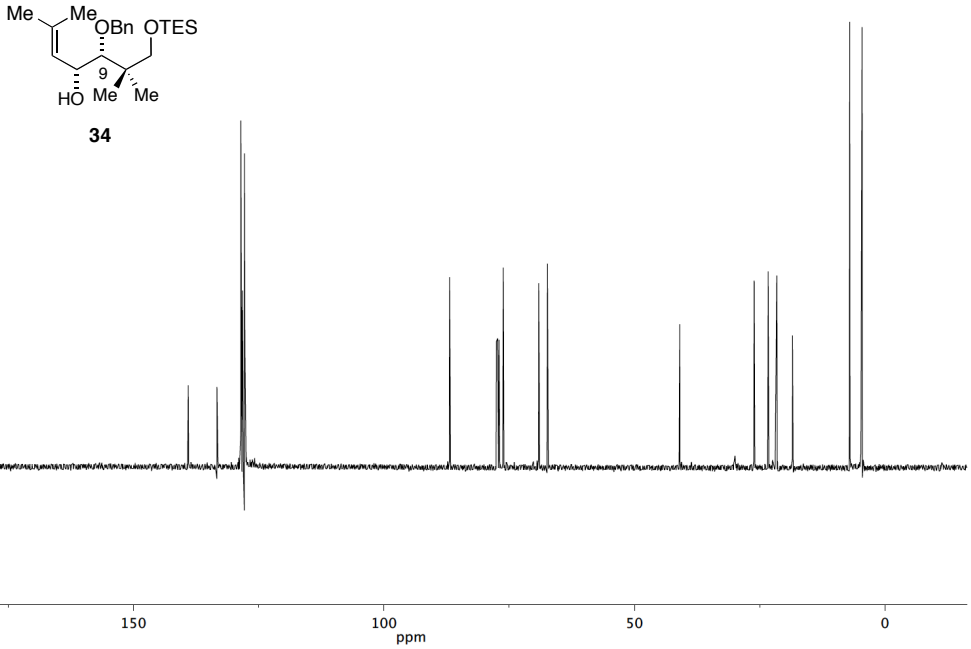
**S2**


O
OBn
OTES
H
7
9
TBSO
Me
Me
22
10
9
8
7
6
5
4
3
2
1
0
ppm

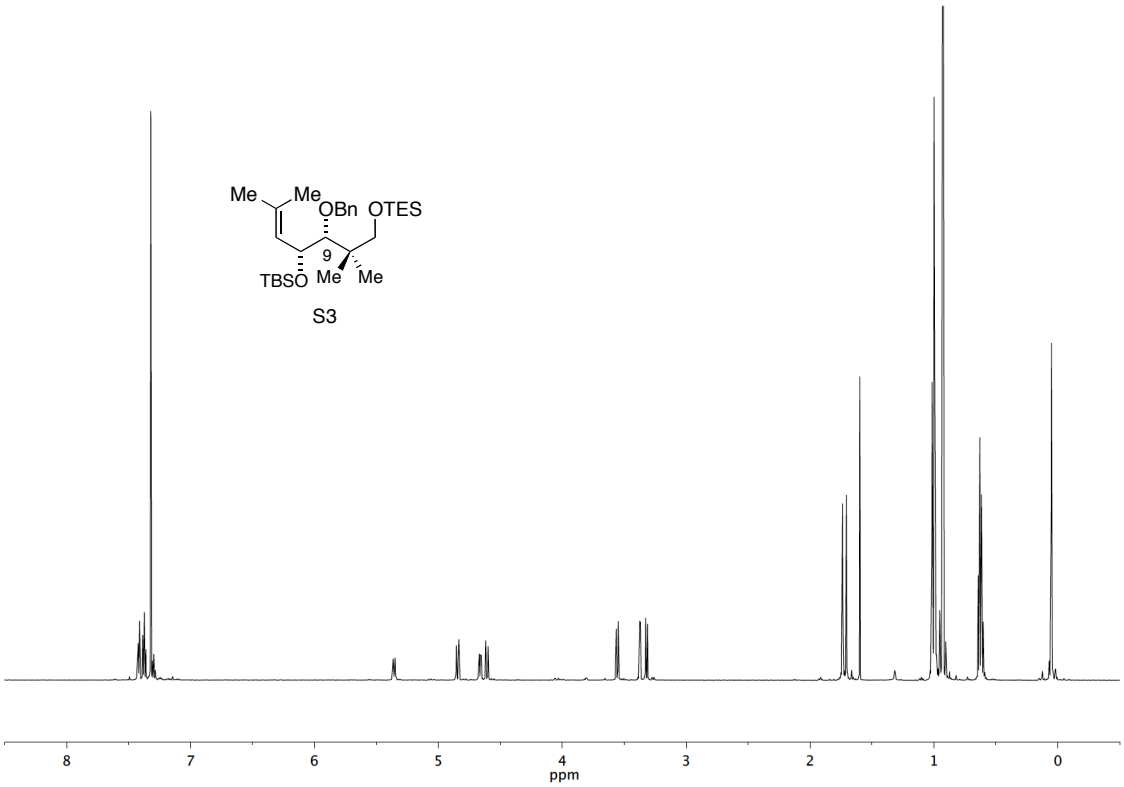

O
OBn
OTES
H
7
9
TBSO
Me
Me
22
200
150
100
50
0
ppm

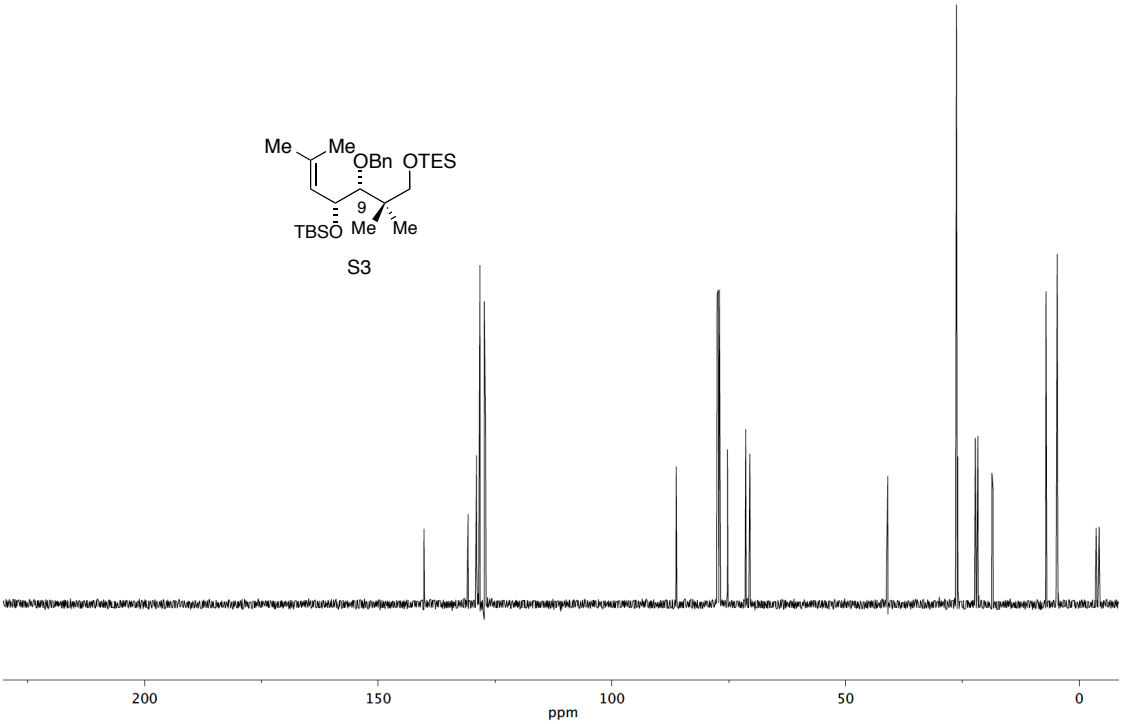

Me
Me
OBn
OTES
9
HO
Me
Me
8
7
6
5
4
3
2
1
0
ppm

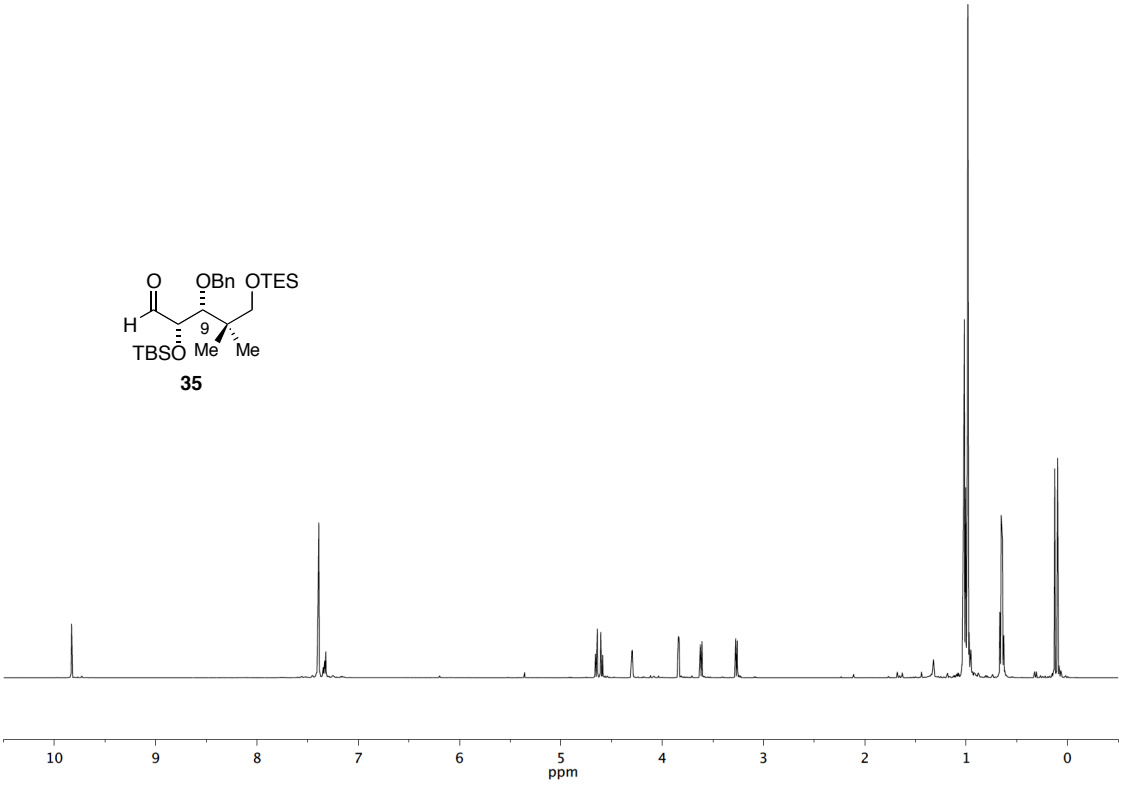
**34**


Me
Me
OBn
OTES
9
HO
Me
Me
200
150
100
50
0
ppm

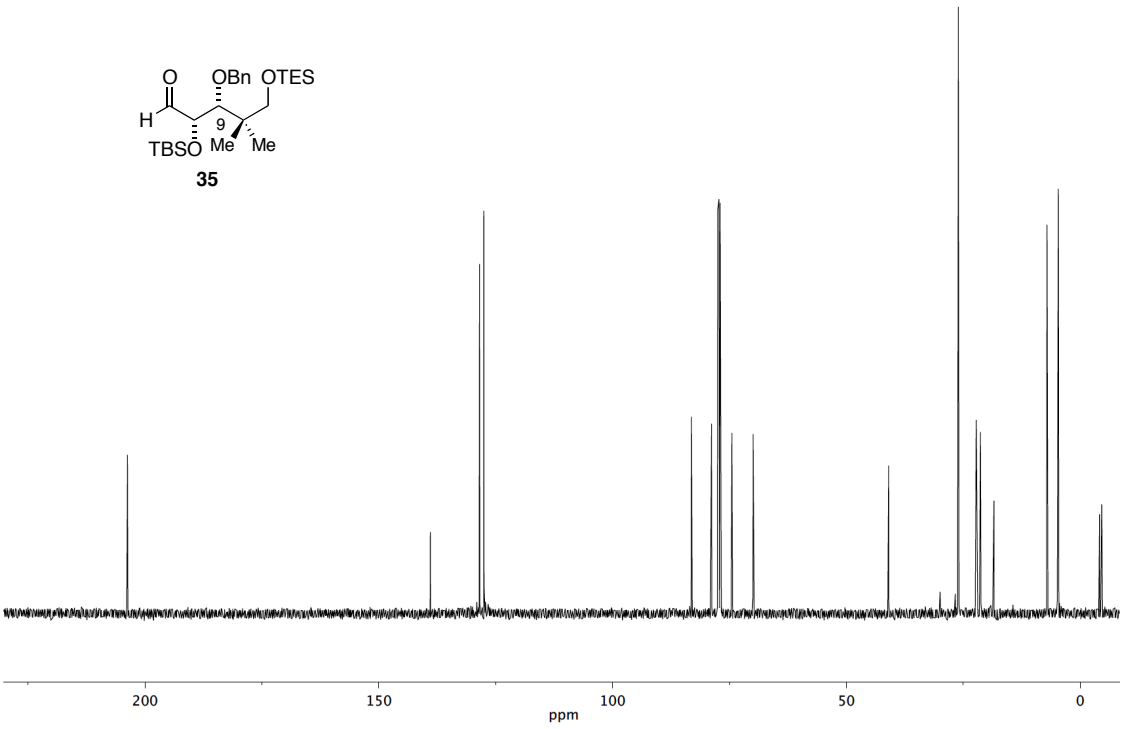
**34**


Me
Me
OBn
OTES
9
TBSO
Me
Me
S3
8
7
6
5
4
3
2
1
0
ppm

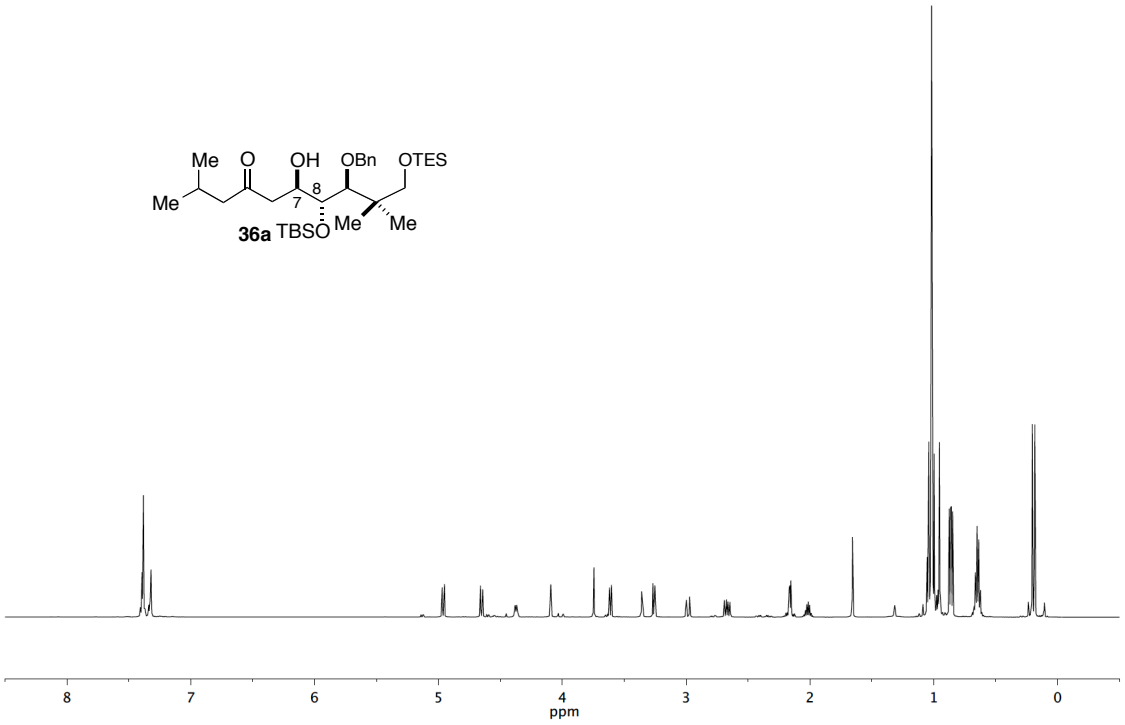

Me
Me
OBn
OTES
9
TBSO
Me
Me
S3
200
150
100
50
0
ppm

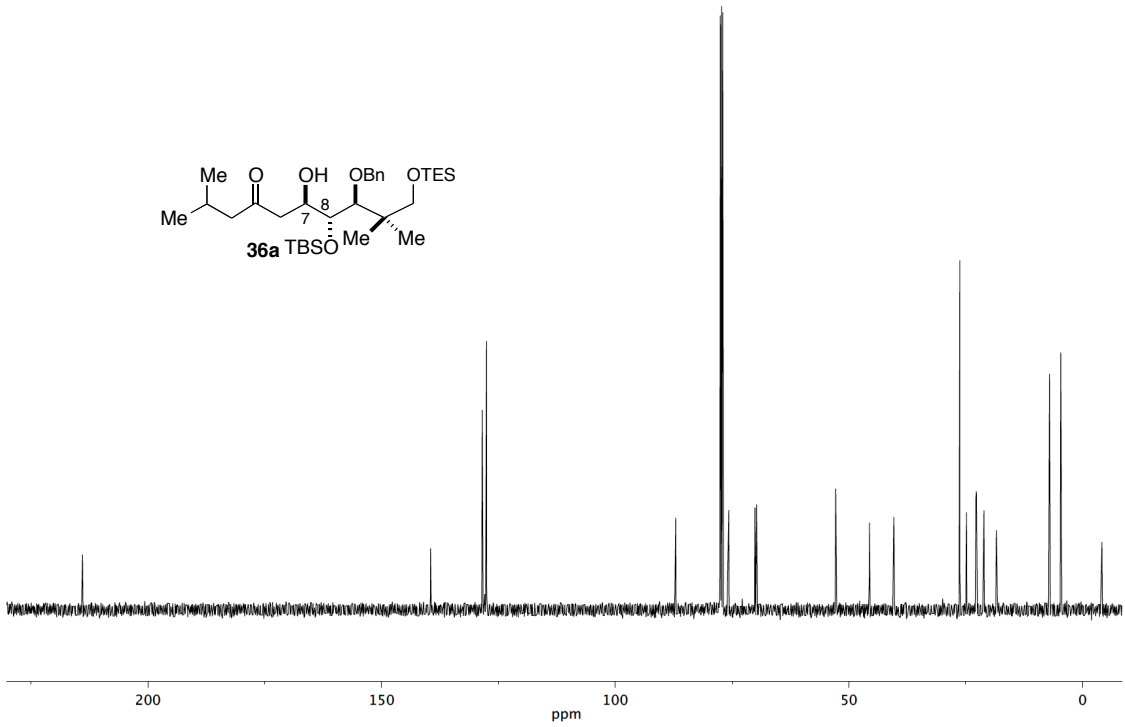

O
OBn
OTES
H
9
TBSO
Me
Me
10
9
8
7
6
5
4
3
2
1
0
ppm

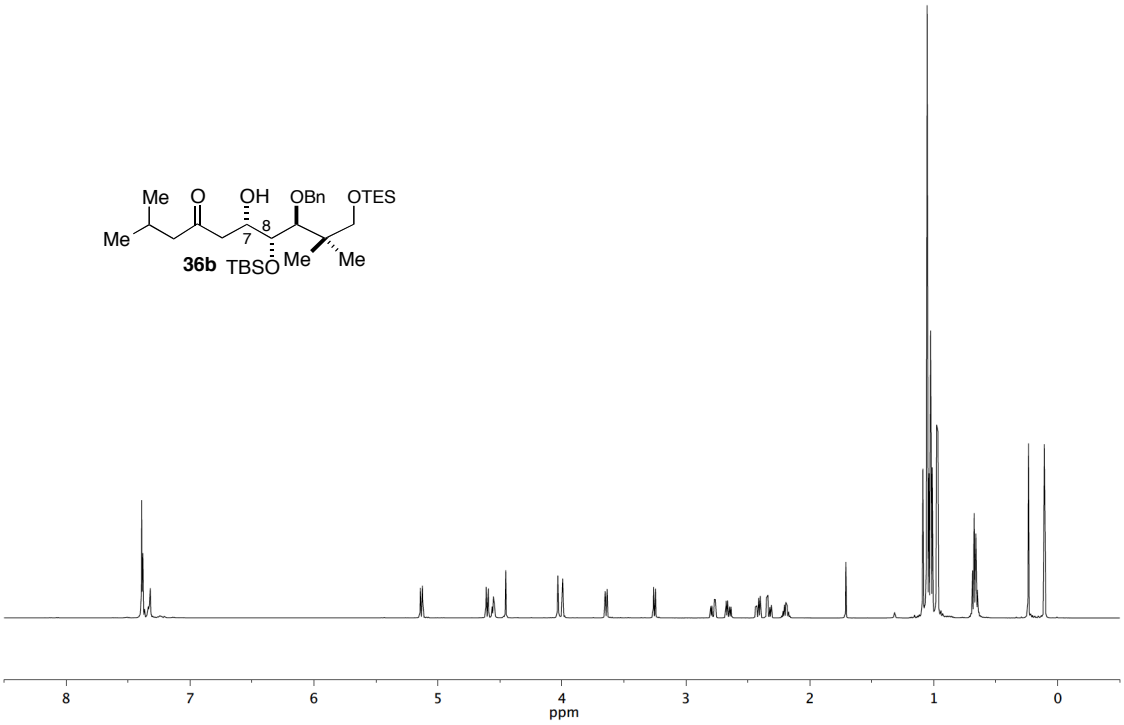
**35**

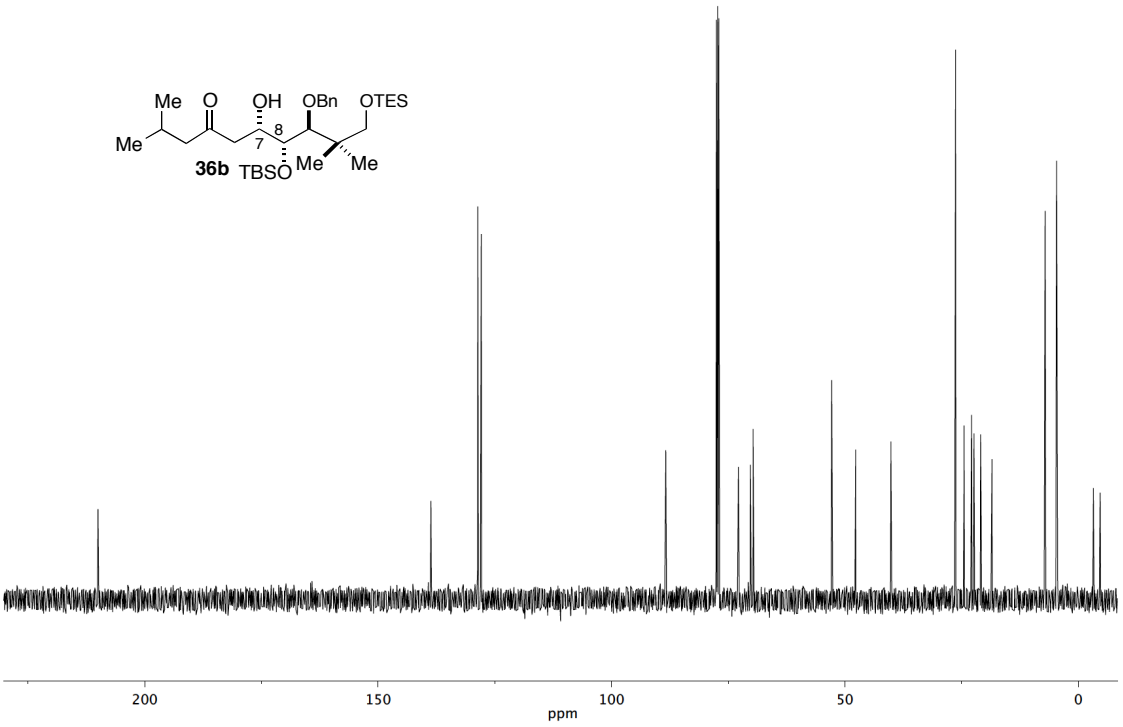

O
OBn
OTES
H
9
TBSO
Me
Me
200
150
100
50
0
ppm

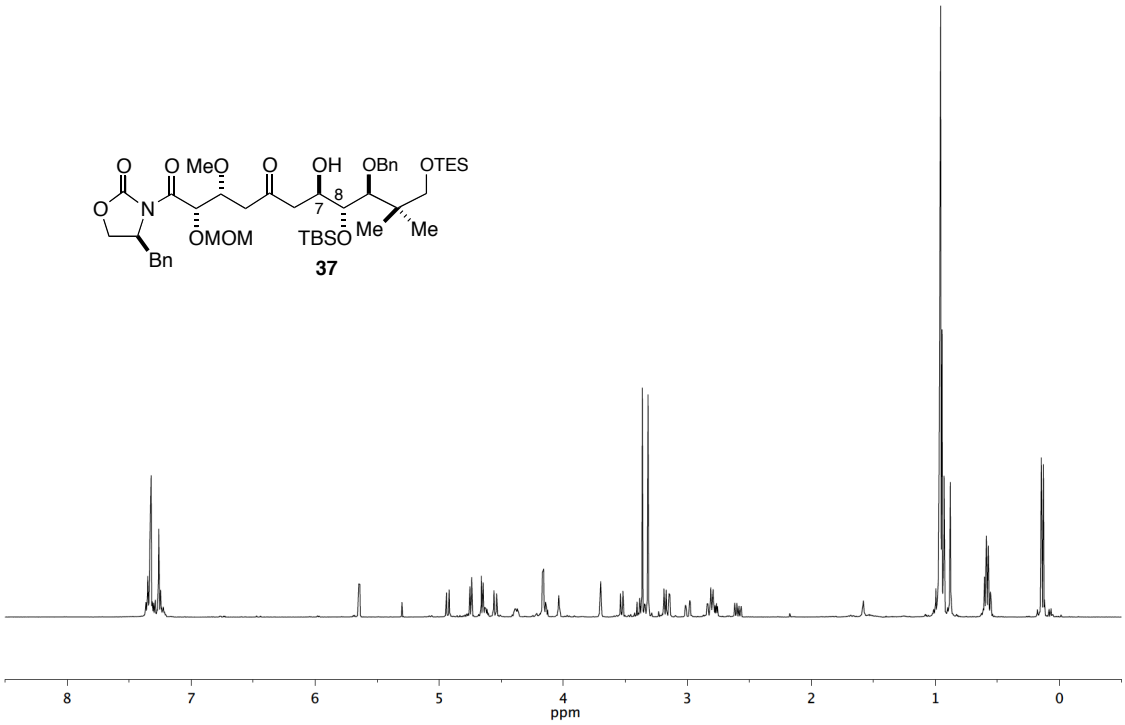
**35**

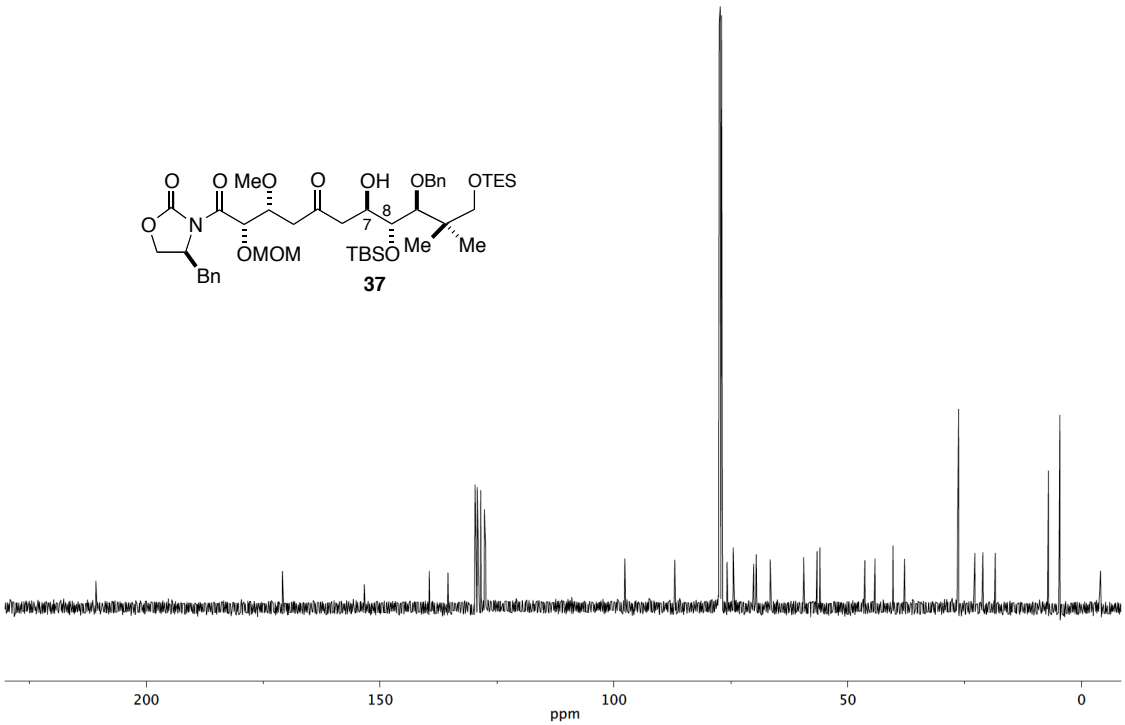

Me
O
OH
OBn
OTES
Me
7
8
36a TBSO
Me
Me
8
7
6
5
4
3
2
1
0
ppm

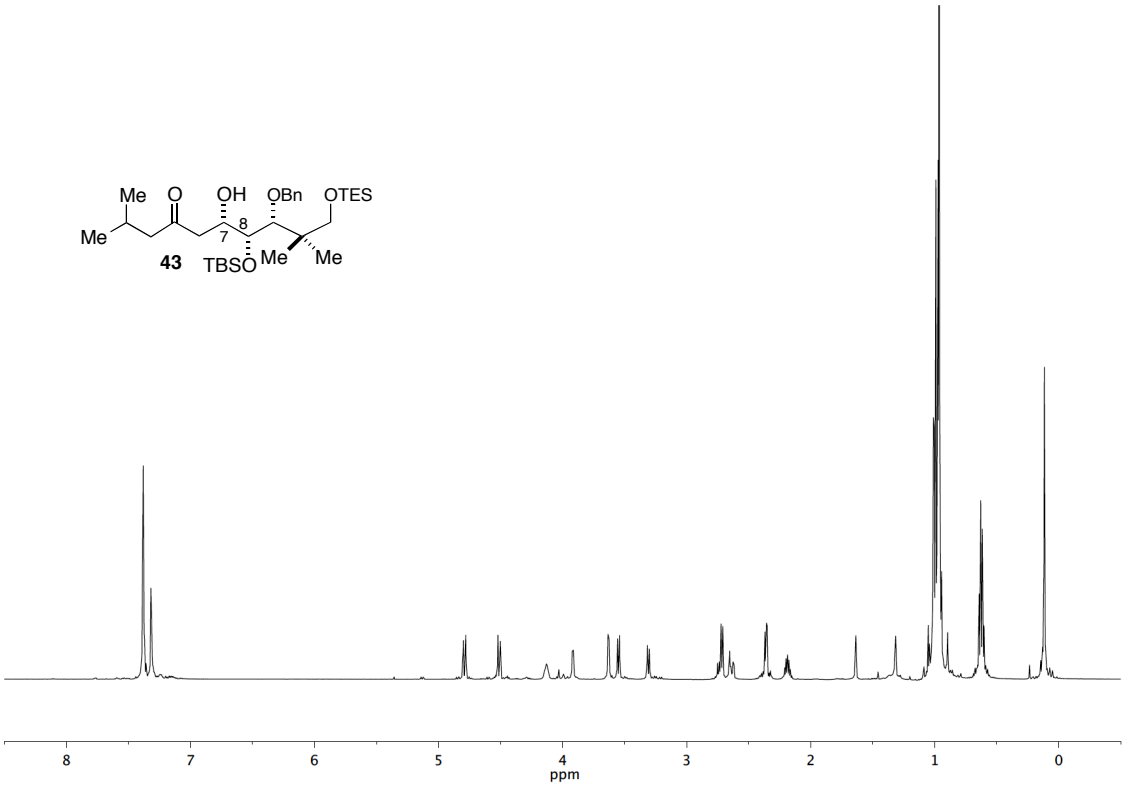

Me
O
OH
OBn
OTES
Me
7
8
36a TBSO
Me
Me
200
150
100
50
0
ppm

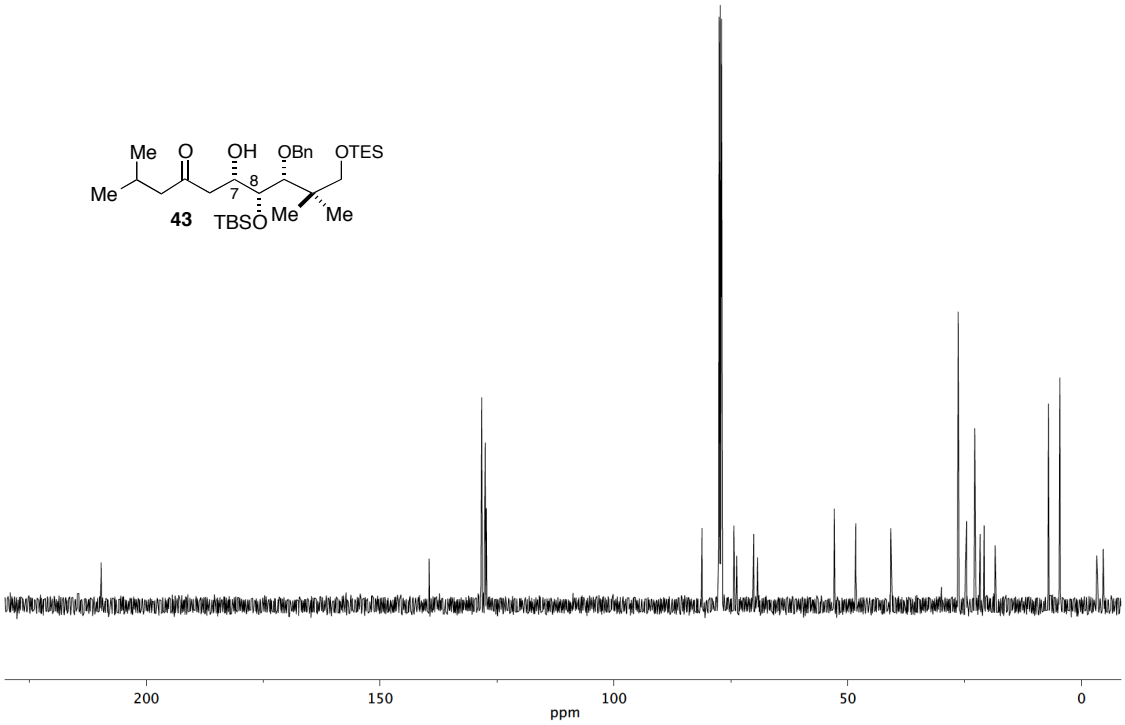

Me
O
OH
OBn
OTES
Me
7
8
36b
TBSO
Me
Me
8
7
6
5
4
3
2
1
0
ppm

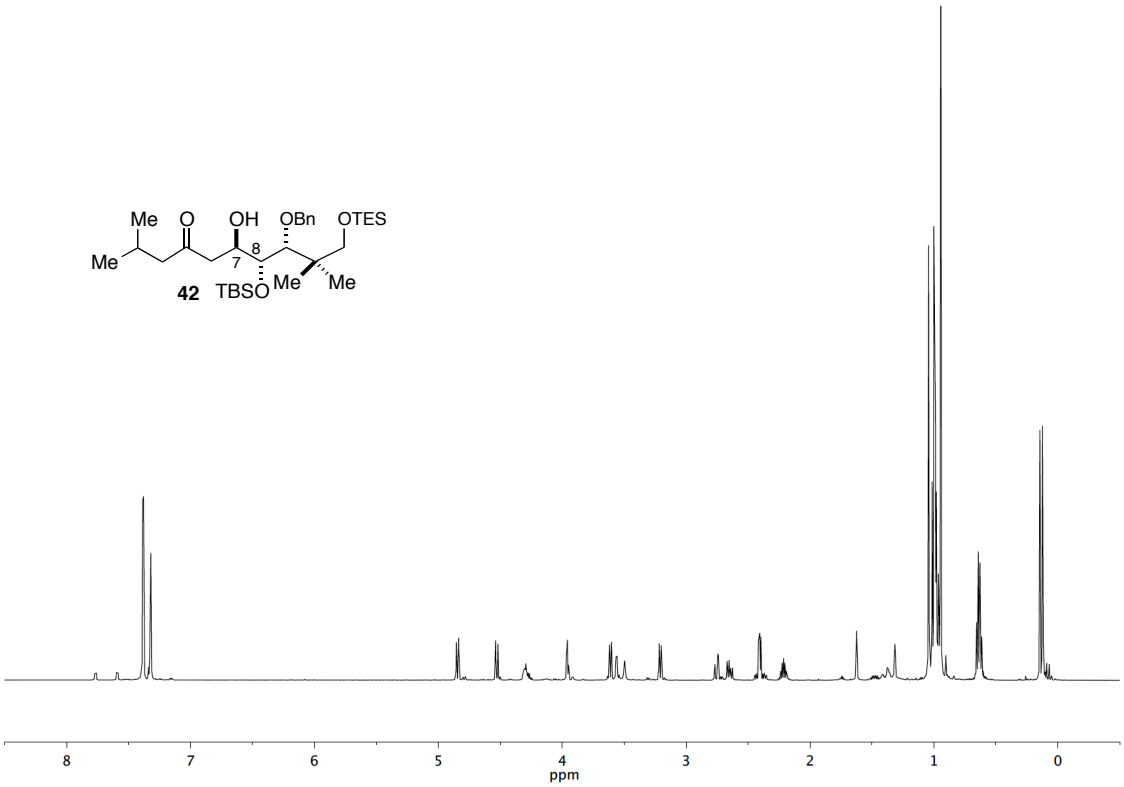

Me
O
OH
OBn
OTES
Me
7
8
36b
TBSO
Me
Me
200
150
100
50
0
ppm

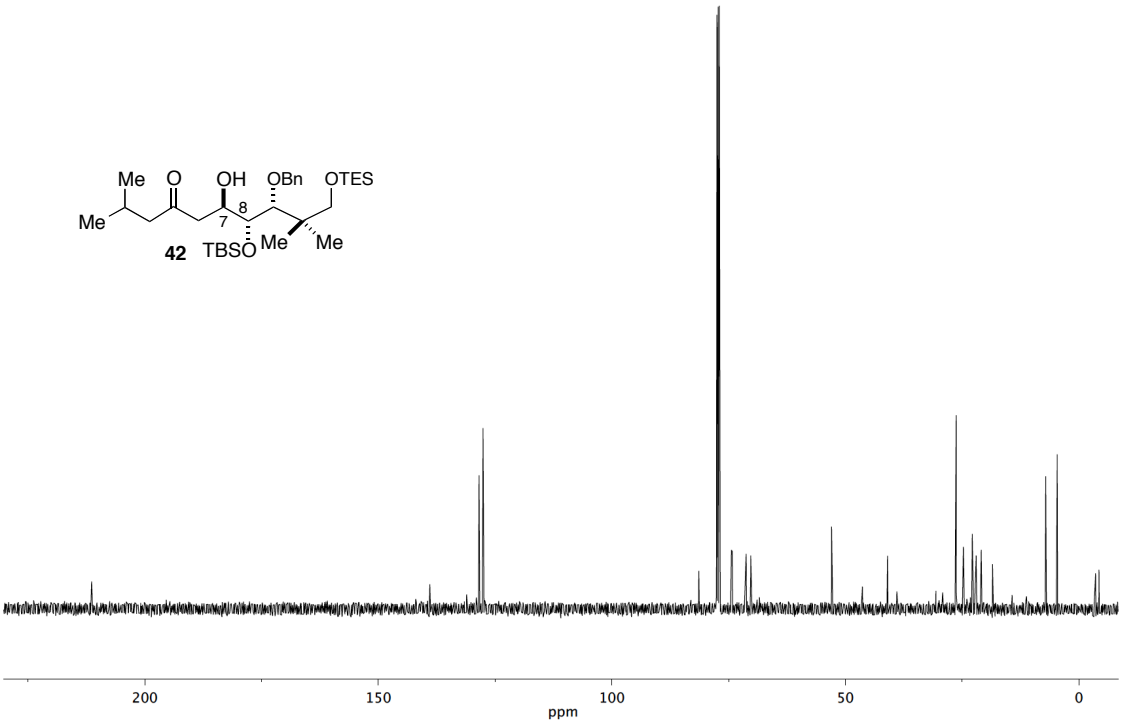

O
O
MeO
O
OH
OBn
OTES
O
N
7
8
OMOM
TBSO
Me
Me
Bn
37
8
7
6
5
4
3
2
1
0
ppm

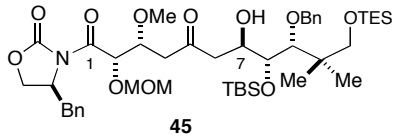

O
O
MeO
O
OH
OBn
OTES
O
N
7
8
OMOM
TBSO
Me
Me
Bn
37
200
150
100
50
0
ppm


Me
O
OH
OBn
OTES
Me
7
8
43
TBSO
Me
Me
8
7
6
5
4
3
2
1
0
ppm


Me
O
OH
OBn
OTES
Me
7
8
43
TBSO
Me
Me
200
150
100
50
0
ppm

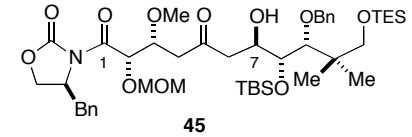

Me
O
OH
OBn
OTES
Me
7
8
Me
Me
42
TBSO
8
7
6
5
4
3
2
1
0
ppm


Me
O
OH
OBn
OTES
Me
7
8
Me
Me
42
TBSO
200
150
100
50
0
ppm


O
O
OMe
O
OH
OBn
OTES
O
N
1
7
OMOM
TBSO
Me
Me
Bn

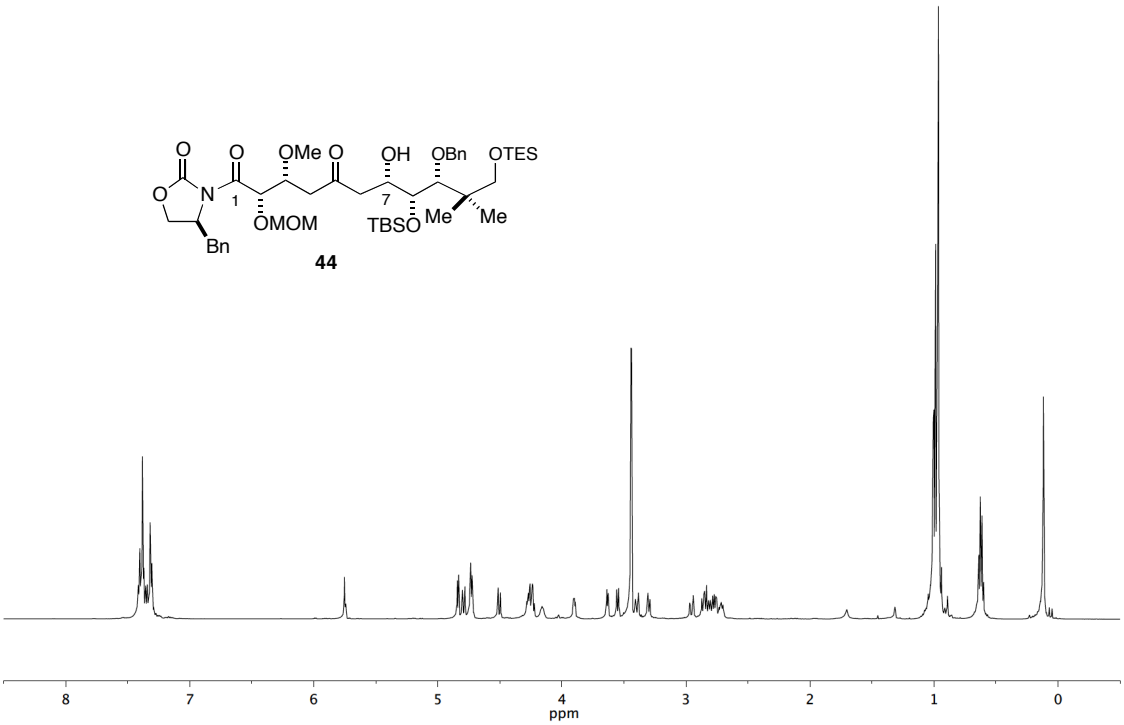
**45**


8
7
6
5
4
3
2
1
0
ppm

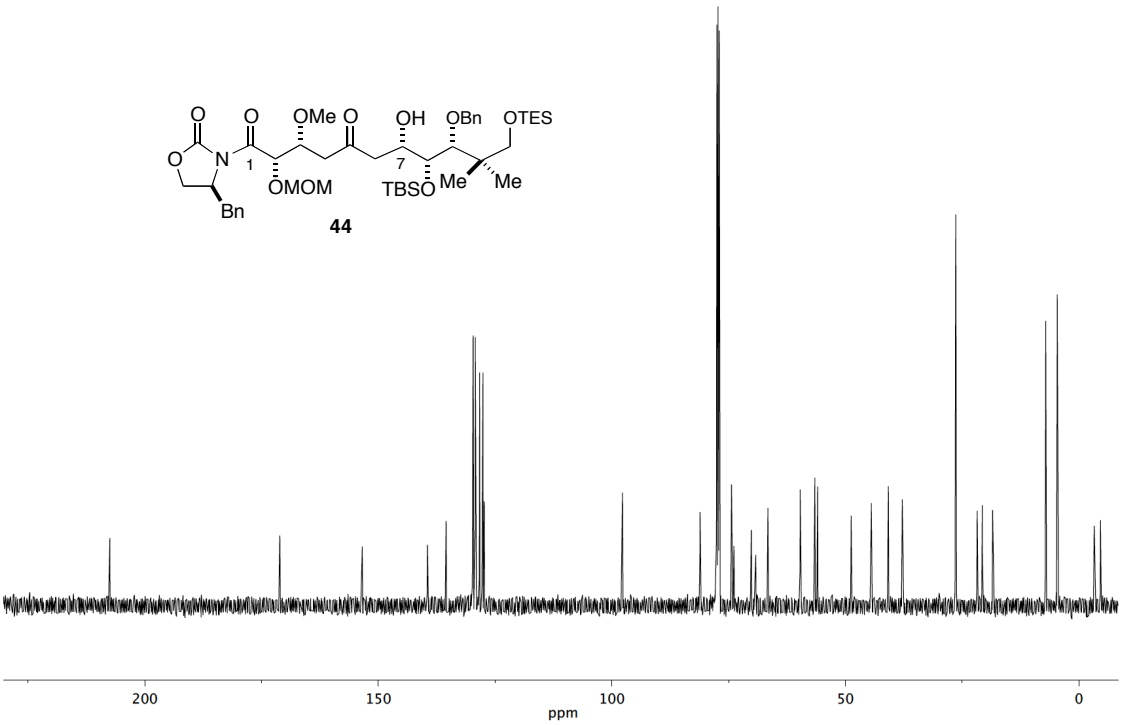

O
O
OMe
O
OH
OBn
OTES
O
N
1
7
OMOM
TBSO
Me
Me
Bn

**45**

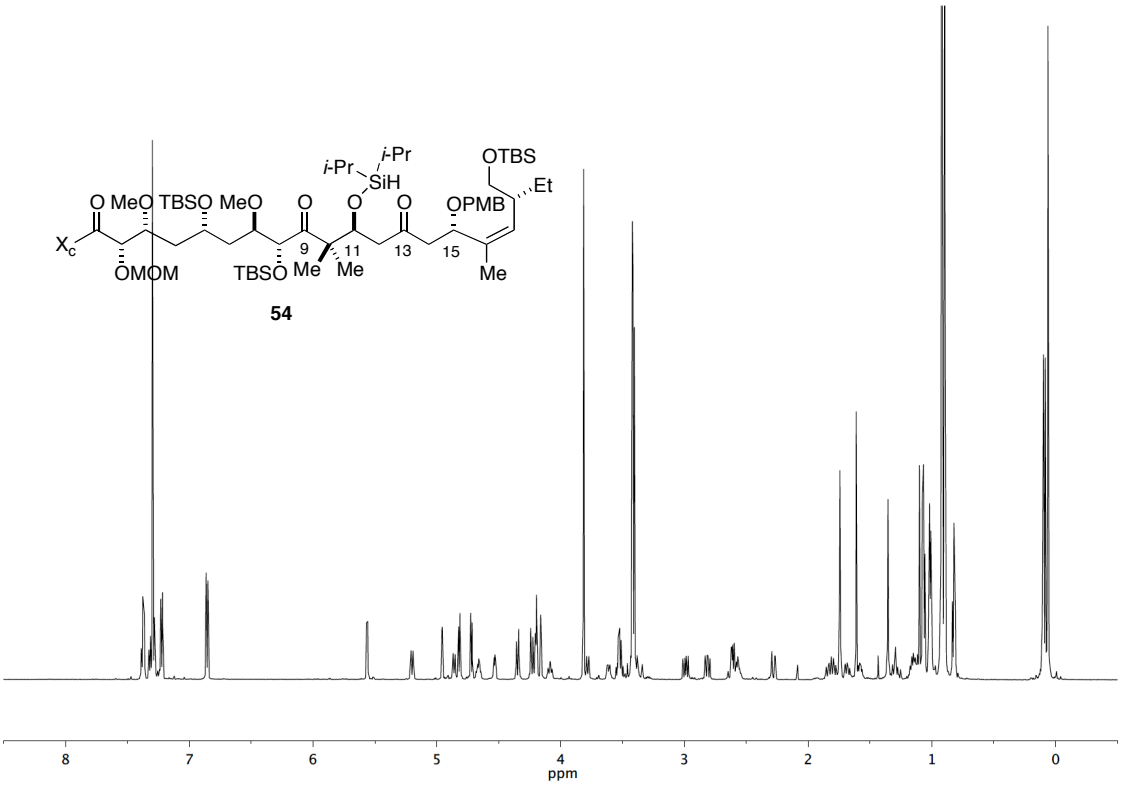

200
150
100
50
0
ppm


O
O
OMe
O
OH
OBn
OTES
O
N
1
7
OMOM
TBSO
Me
Me
Bn
8
7
6
5
4
3
2
1
0
ppm

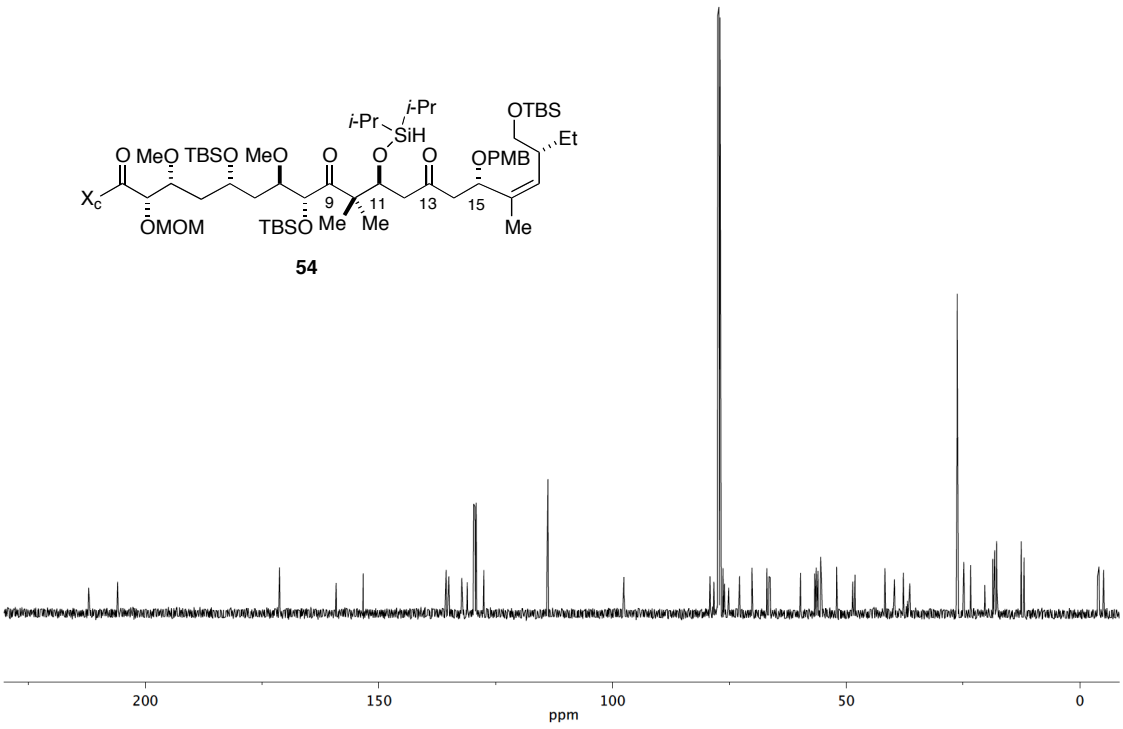
**44**


O
O
OMe
O
OH
OBn
OTES
O
N
1
7
OMOM
TBSO
Me
Me
Bn
200
150
100
50
0
ppm

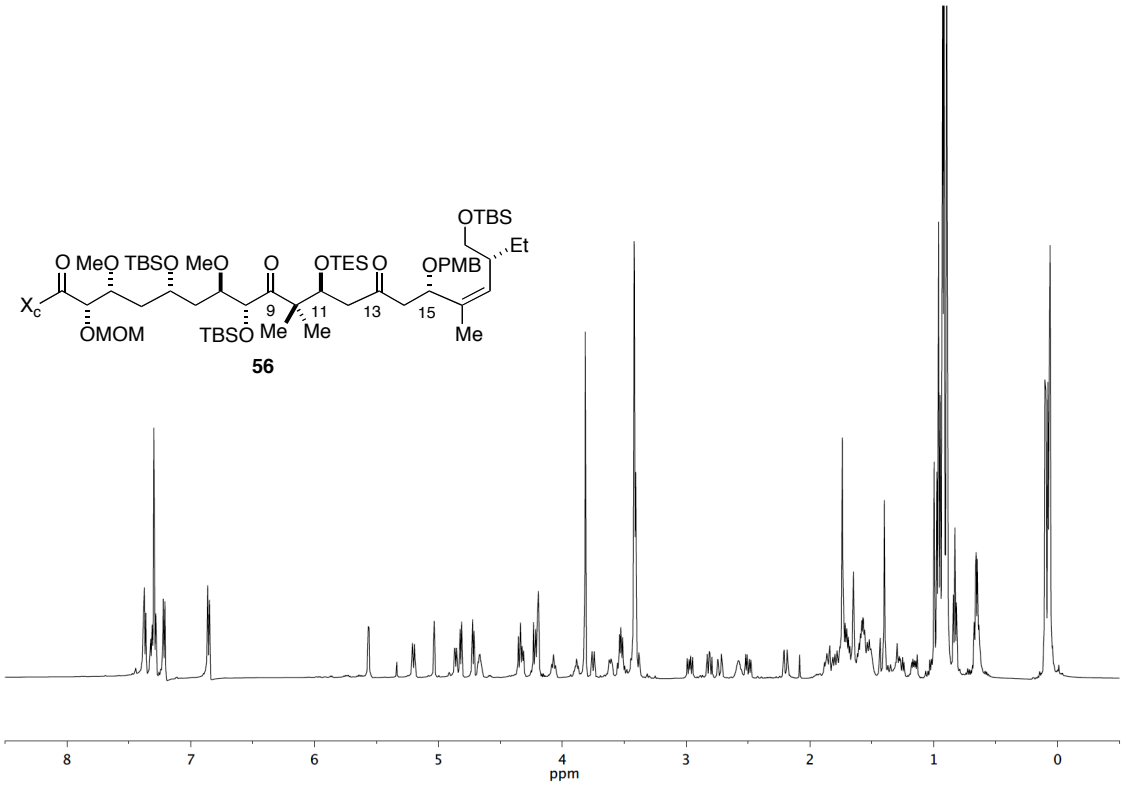
**44**

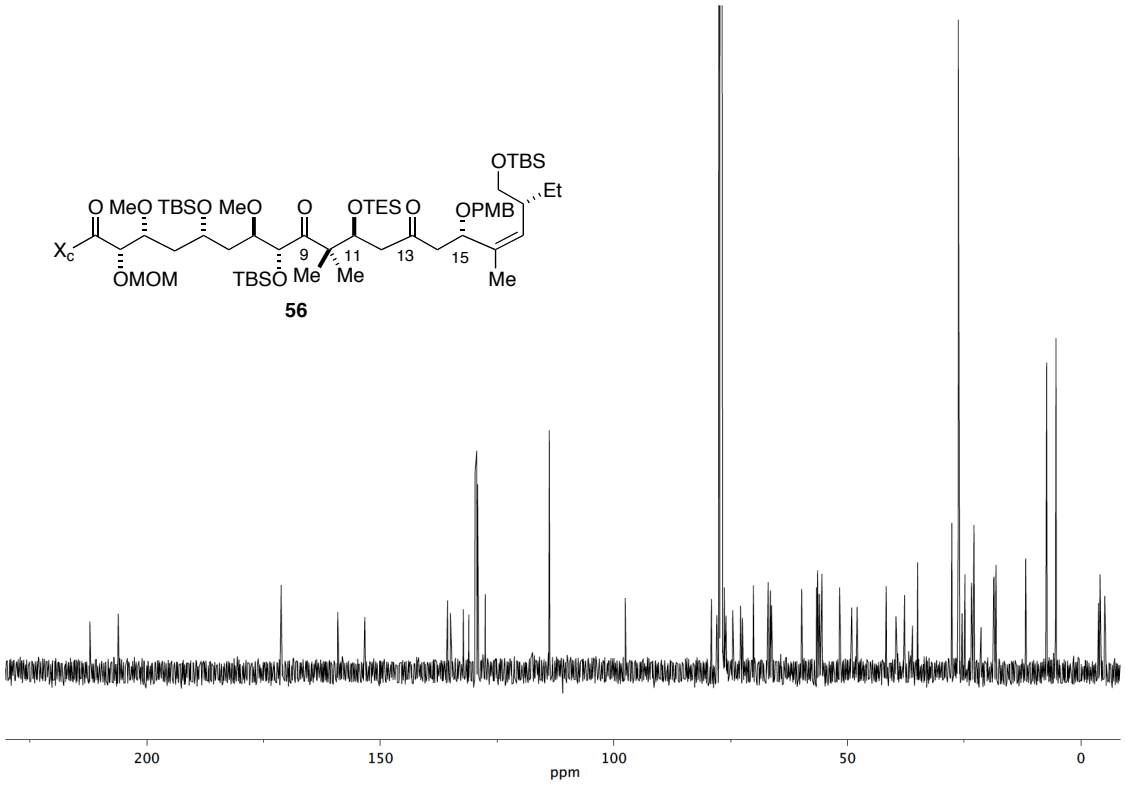

i-Pr
i-Pr
SiH
OTBS
Et
O MeO TBSO MeO
O
O
O
OPMB
X_c
9
11
13
15
OMOM
TBSO Me
Me
Me
Me
8
7
6
5
4
3
2
1
0
ppm

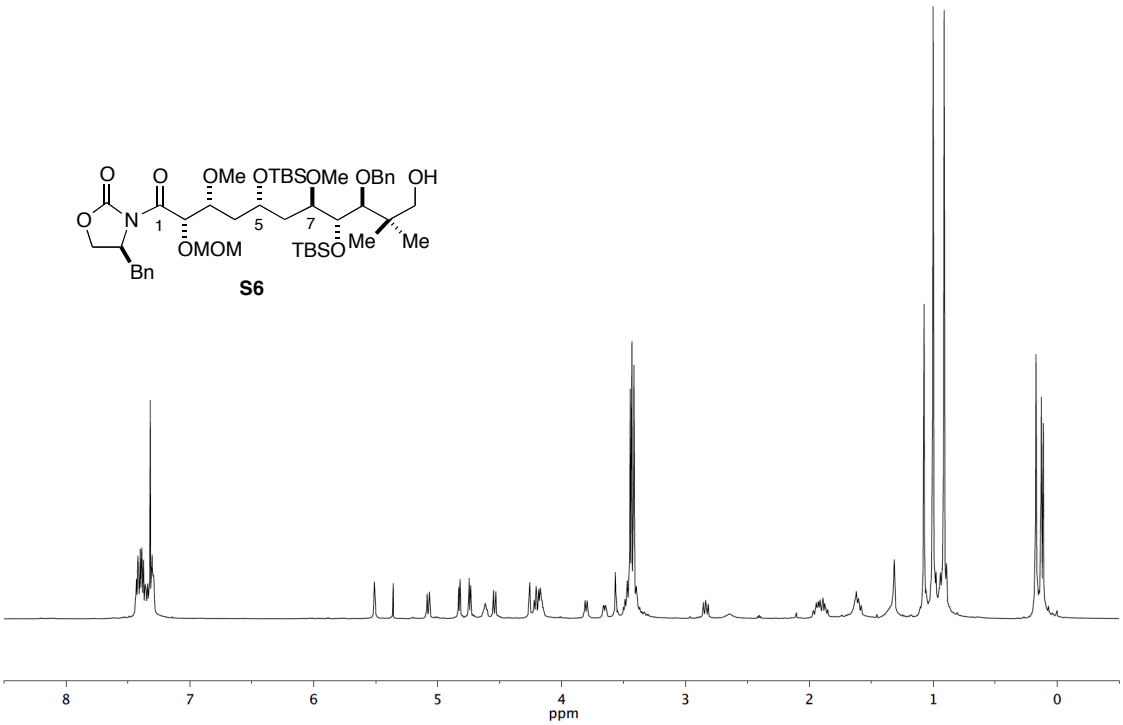
**54**

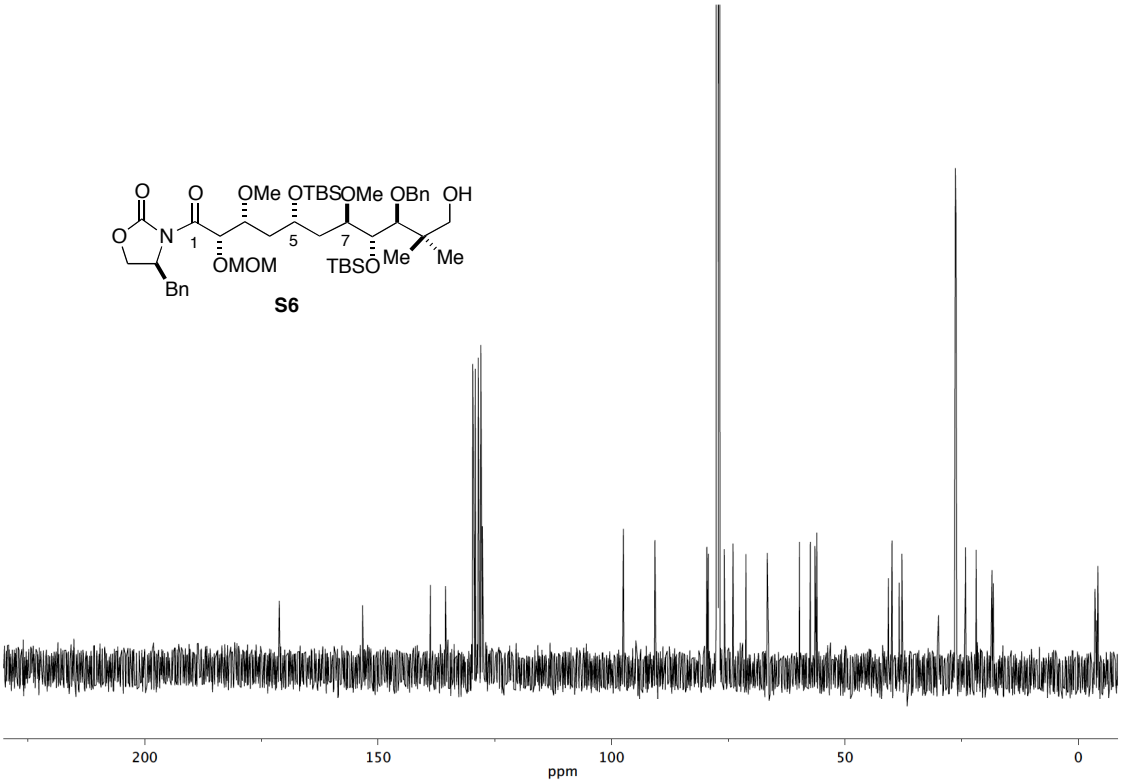

i-Pr
i-Pr
SiH
OTBS
Et
O MeO TBSO MeO
O
O
O
OPMB
X_c
9
11
13
15
OMOM
TBSO Me
Me
Me
200
150
100
50
0
ppm

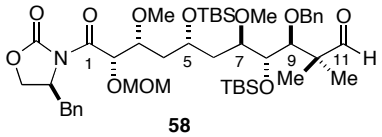
**54**


OTBS
Et
O MeO TBSO MeO O OTES O OPMB
Xc
OMOM
TBSO
9
11
13
15
Me
Me
Me
56
8
7
6
5
4
3
2
1
0
ppm


OTBS
Et
O MeO TBSO MeO O OTES O OPMB
Xc
OMOM
TBSO
9
11
13
15
Me
Me
Me
56
200
150
100
50
0
ppm

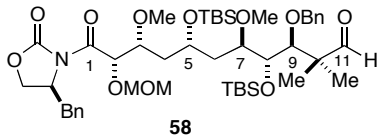

OMe
OTBS
OMe
OBn
OH
OMOM
TBSO
Me
Me
Bn
1
5
7
S6
8
7
6
5
4
3
2
1
0
ppm


OMe
OTBS
OMe
OBn
OH
OMOM
TBSO
Me
Me
Bn
1
5
7
S6
200
150
100
50
0
ppm


O
O
OMe
OTBS
OMe
OBn
O
O
N
1
5
7
9
11
H
OMOM
TBSO
Me
Me
Bn

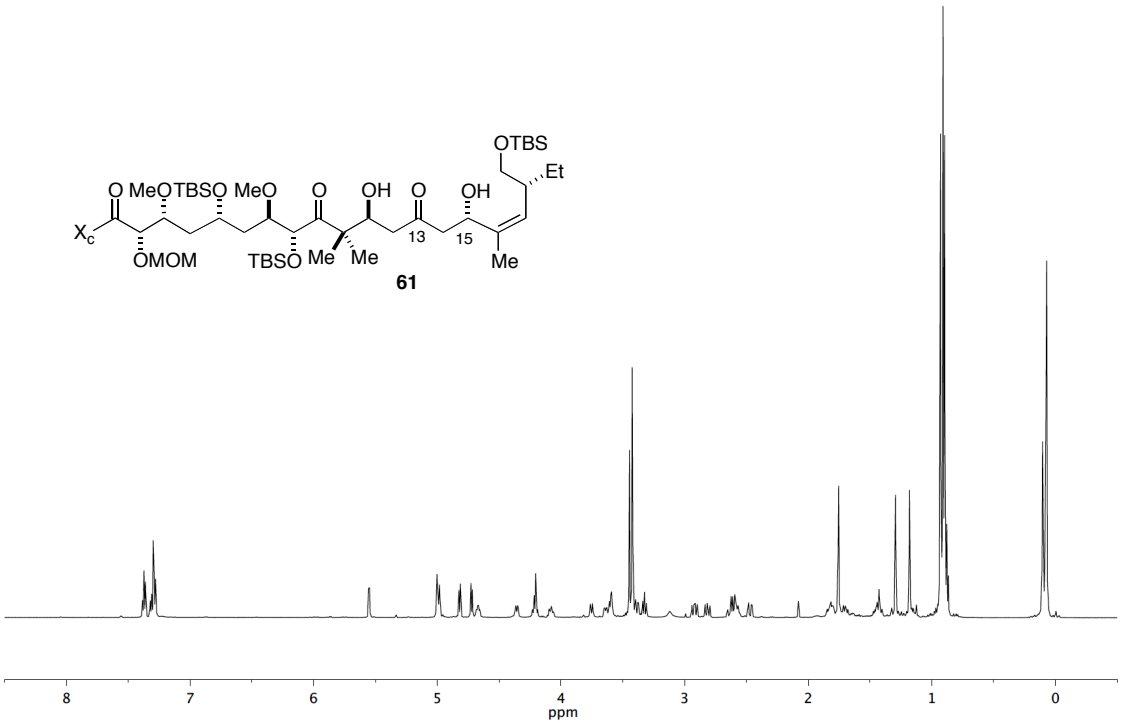
**58**

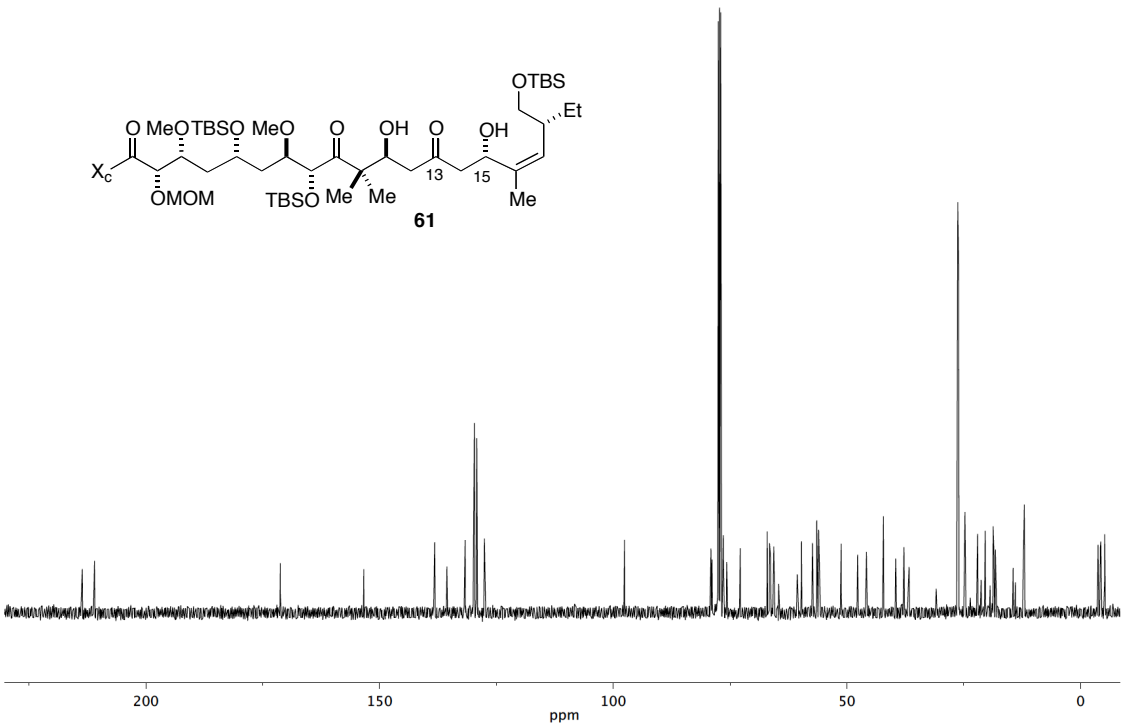

10
9
8
7
6
5
4
3
2
1
0
ppm

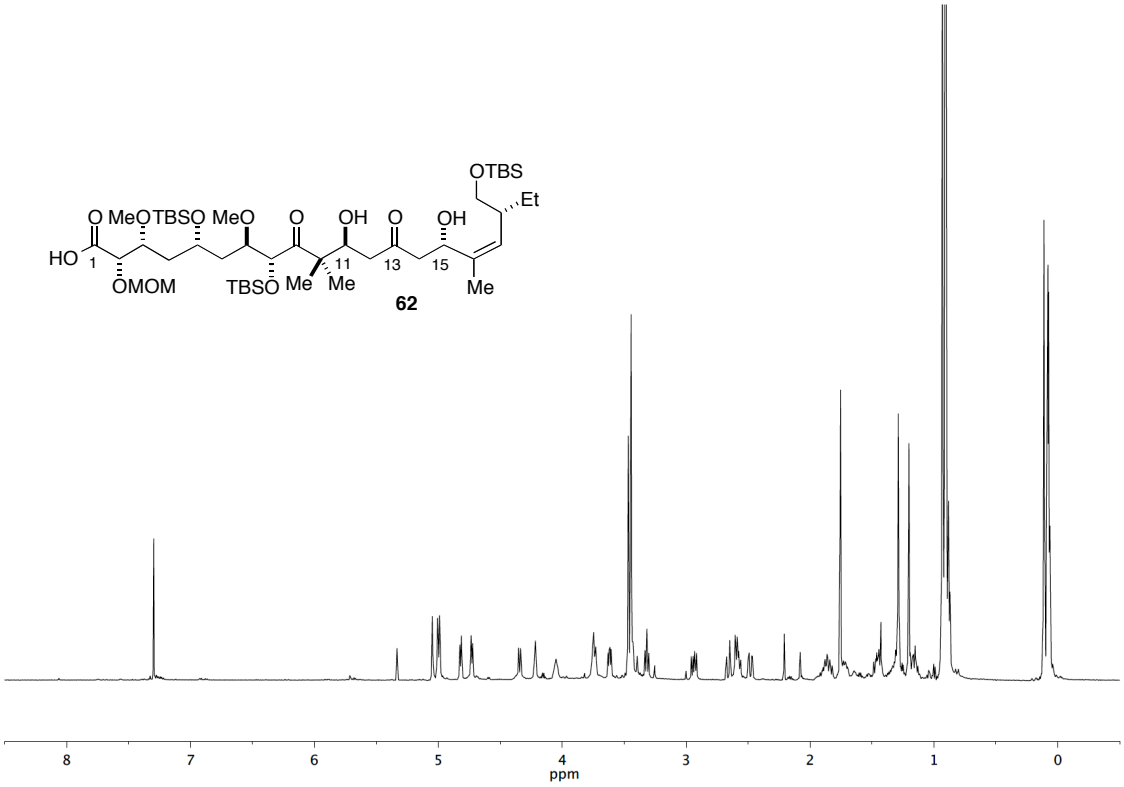

O
O
OMe
OTBS
OMe
OBn
O
O
N
1
5
7
9
11
H
OMOM
TBSO
Me
Me
Bn

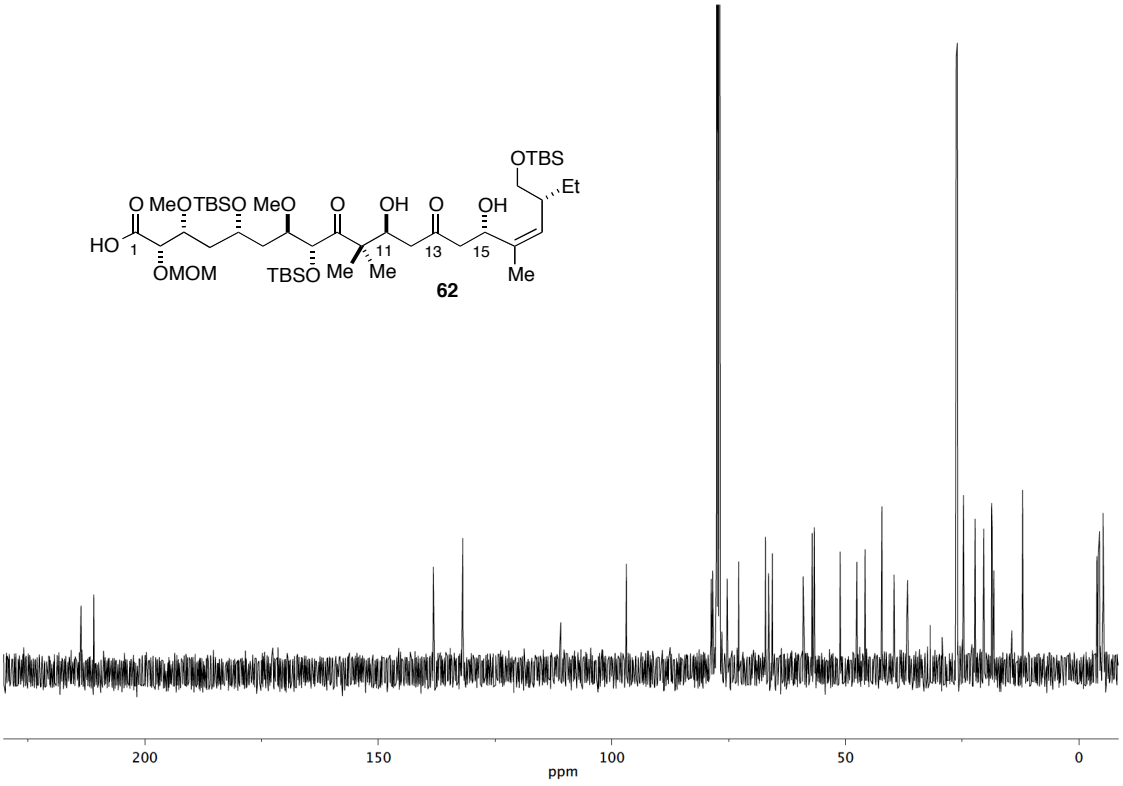
**58**

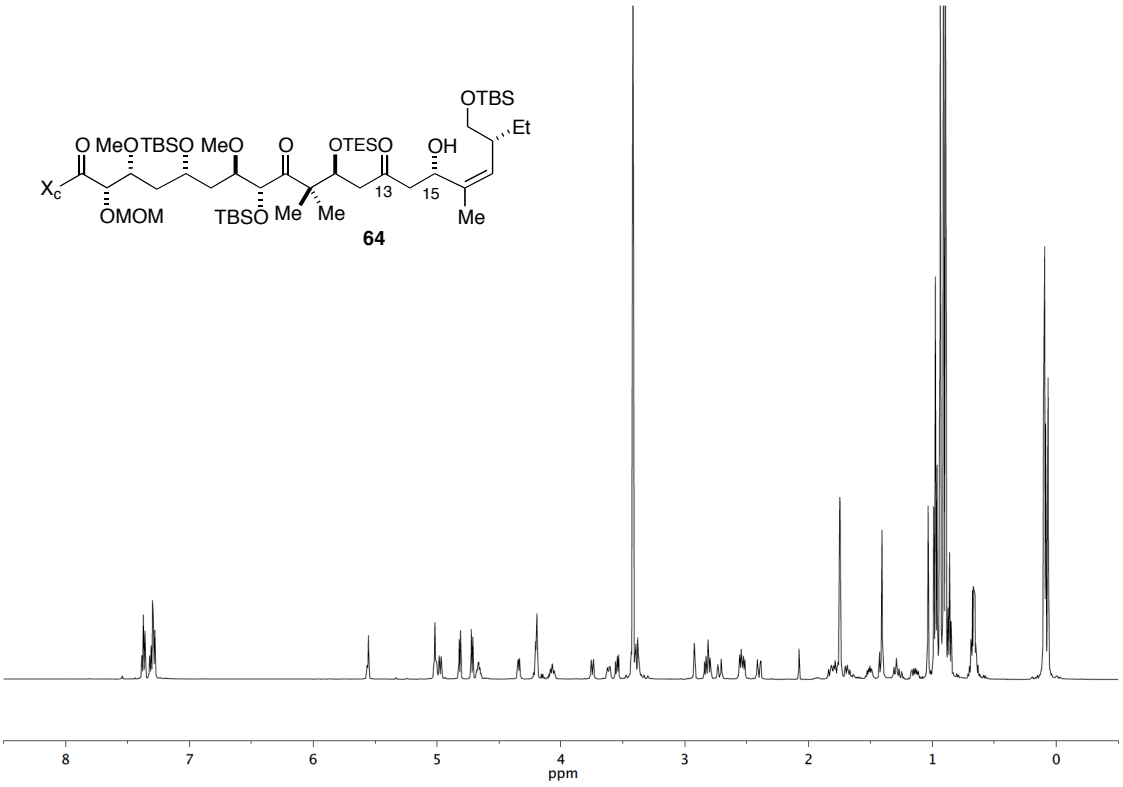

200
150
100
50
0
ppm

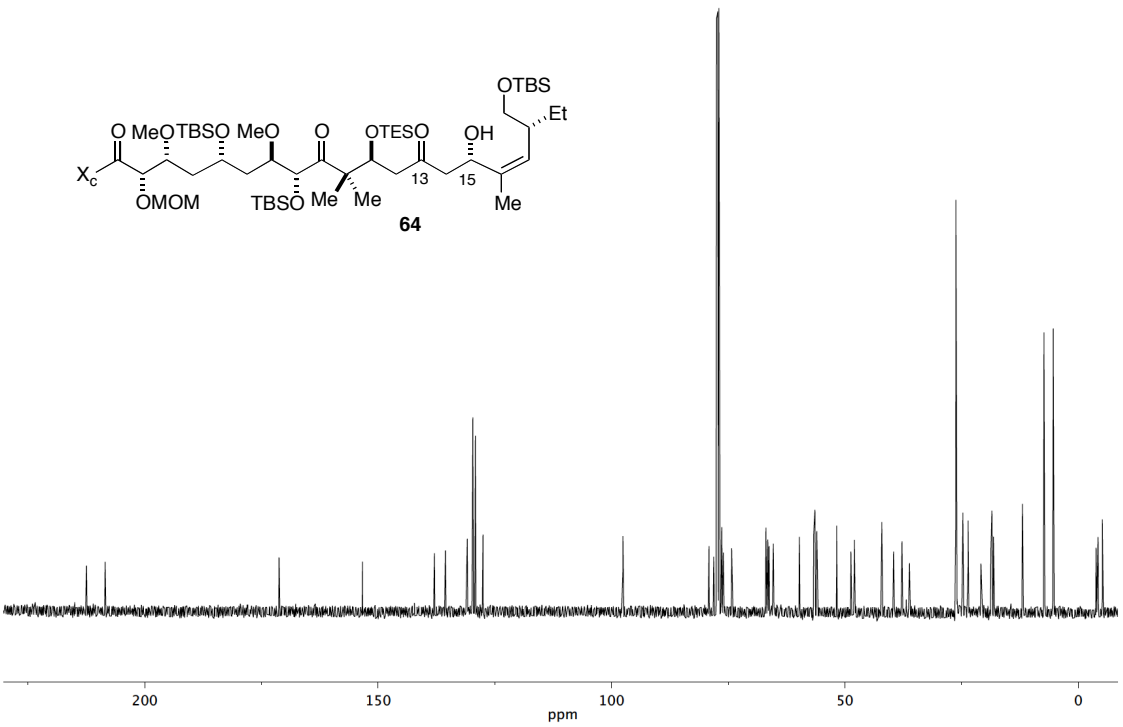

OTBS
Et
O MeO TBSO MeO O OH O OH
Xc
13
15
OMOM
TBSO Me Me
Me
61
8
7
6
5
4
3
2
1
0
ppm

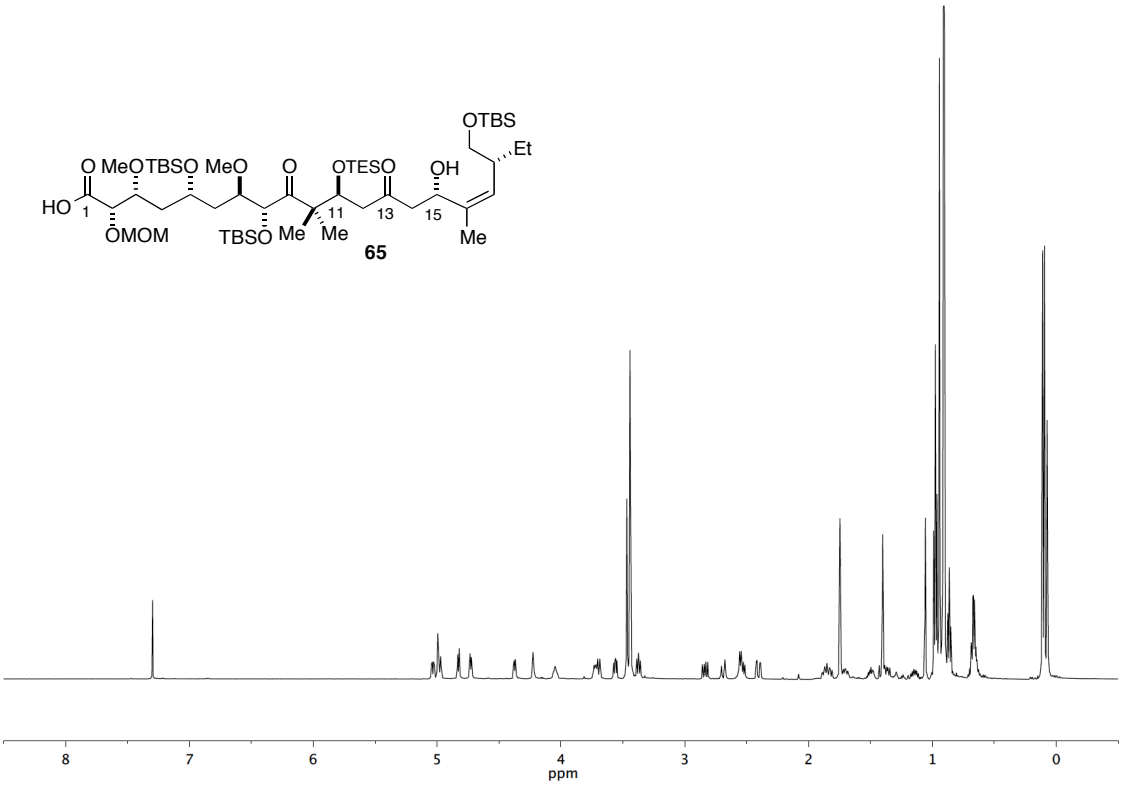

OTBS
Et
O MeO TBSO MeO O OH O OH
Xc
13
15
OMOM
TBSO Me Me
Me
61
200
150
100
50
0
ppm

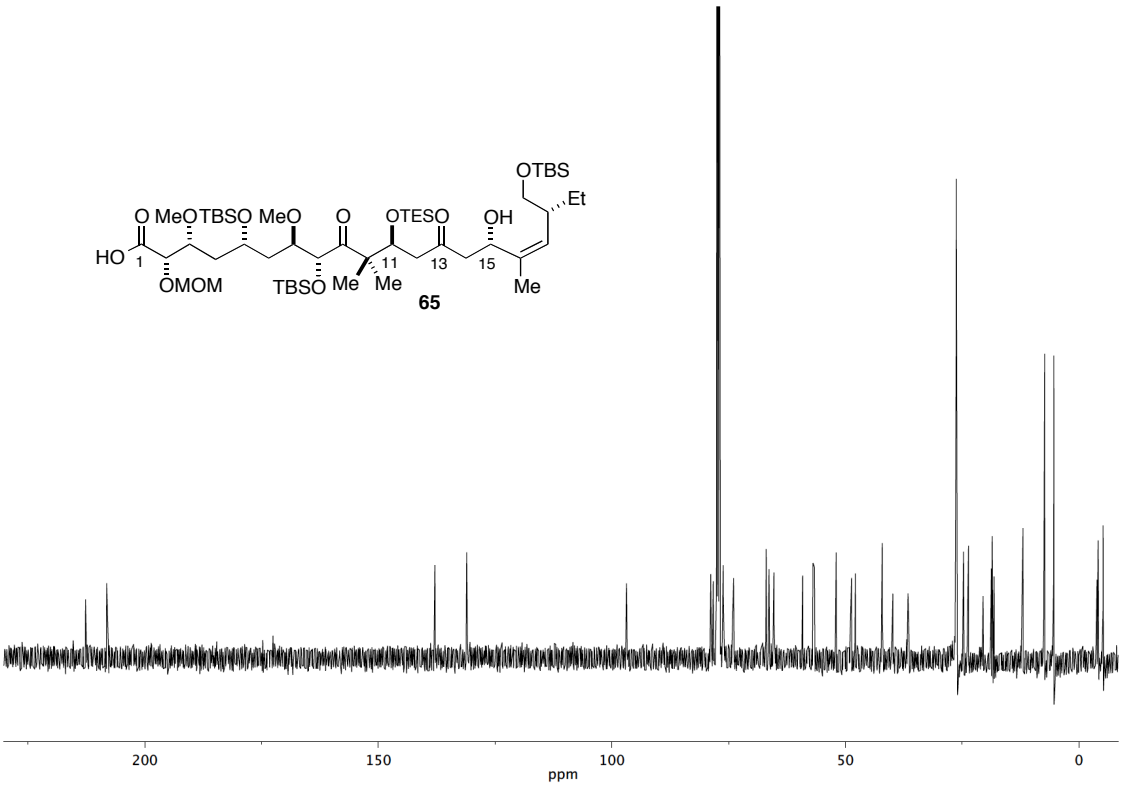

OTBS
Et
O MeO TBSO MeO O OH O OH
HO 1
11 13 15
OMOM TBSO Me Me Me
62
8 7 6 5 4 3 2 1 0
ppm

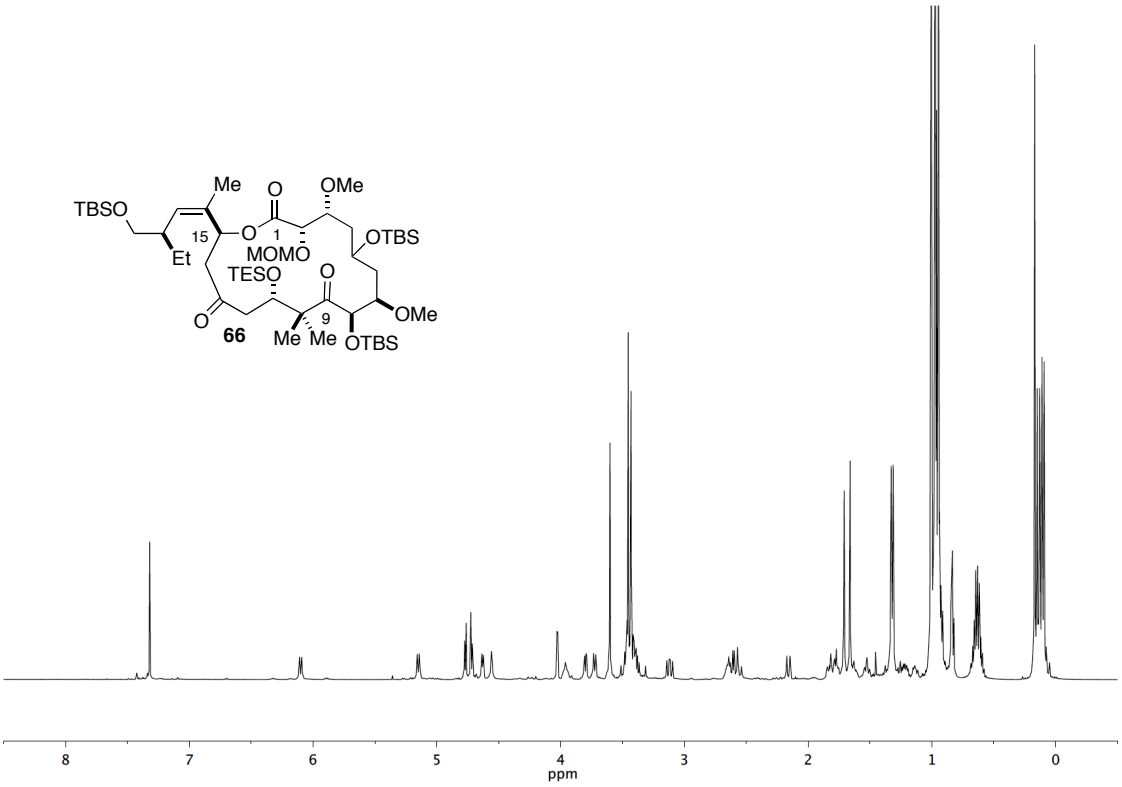

OTBS
Et
O MeO TBSO MeO O OH O OH
HO 1
11 13 15
OMOM TBSO Me Me Me
62
200 150 100 50 0
ppm

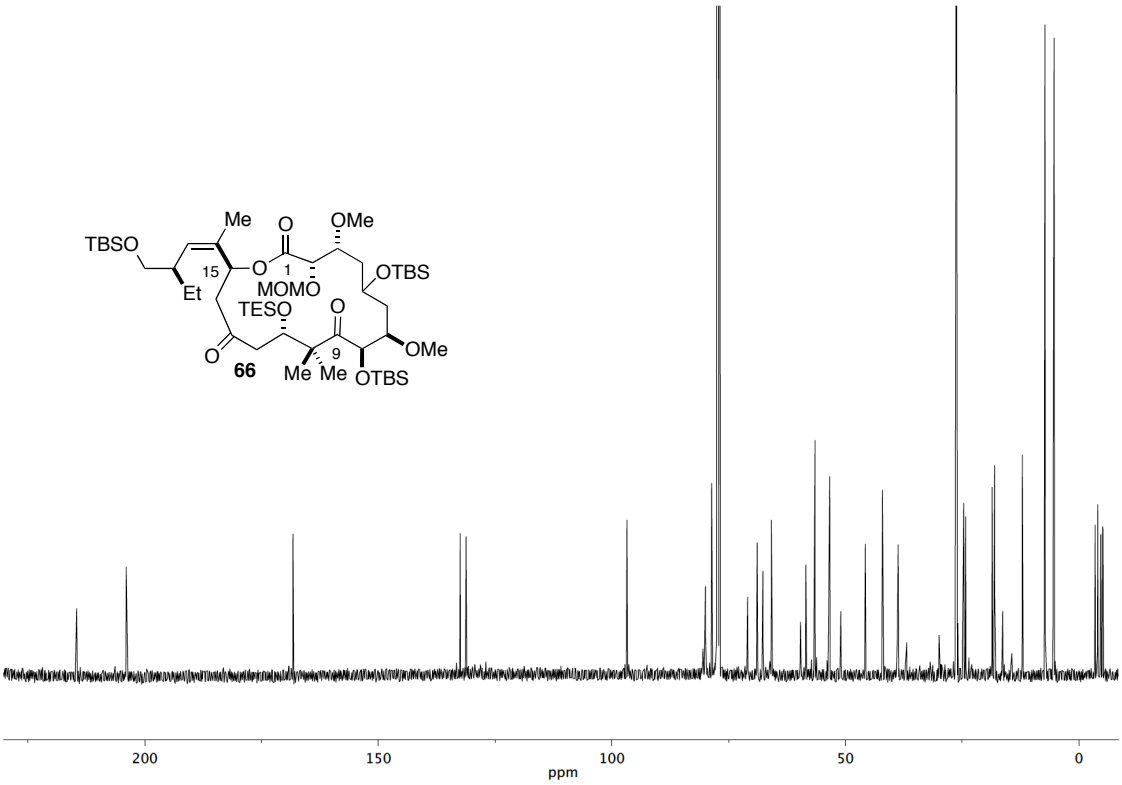

OTBS
Et
O MeO TBSO MeO O OTESO OH
Xc
OMOM
TBSO Me Me
13
15
Me
64
8
7
6
5
4
3
2
1
0
ppm

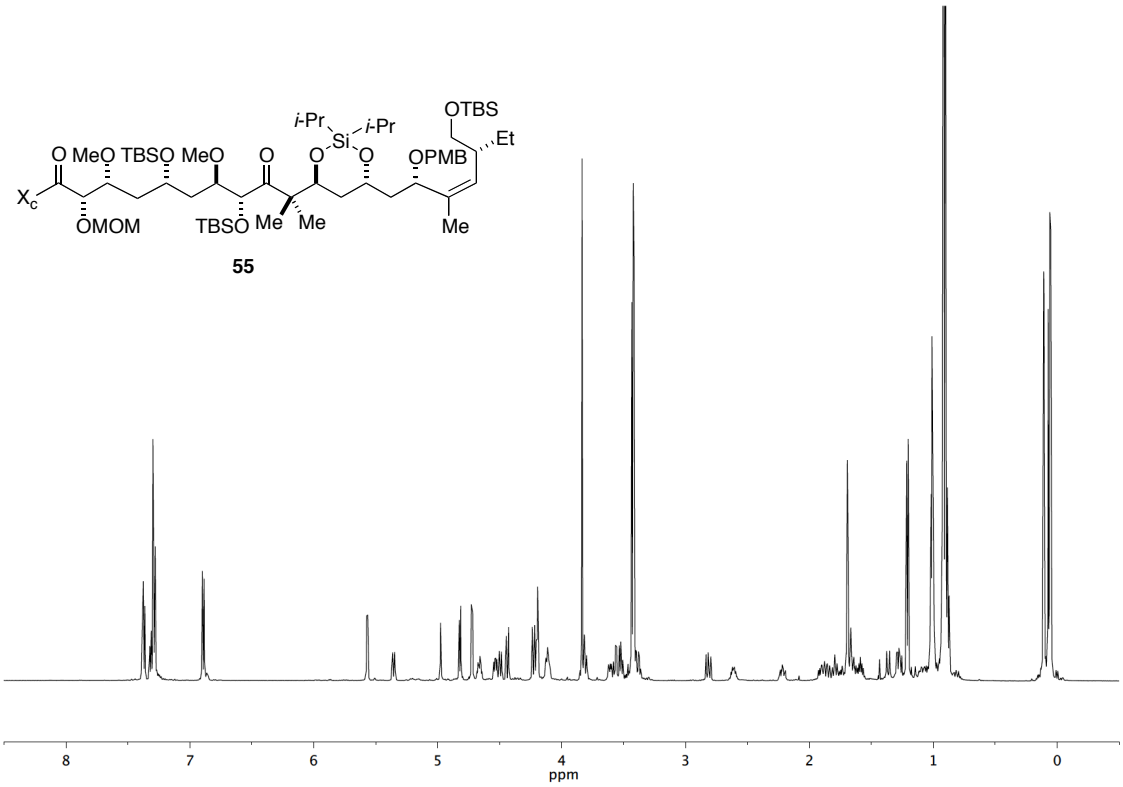

OTBS
Et
O MeO TBSO MeO O OTESO OH
Xc
OMOM
TBSO Me Me
13
15
Me
64
200
150
100
50
0
ppm


OTBS
Et
O MeO TBSO MeO O OTESO OH
HO 1
11
13
15
OMOM
TBSO Me Me
Me
65
8
7
6
5
4
3
2
1
0
ppm

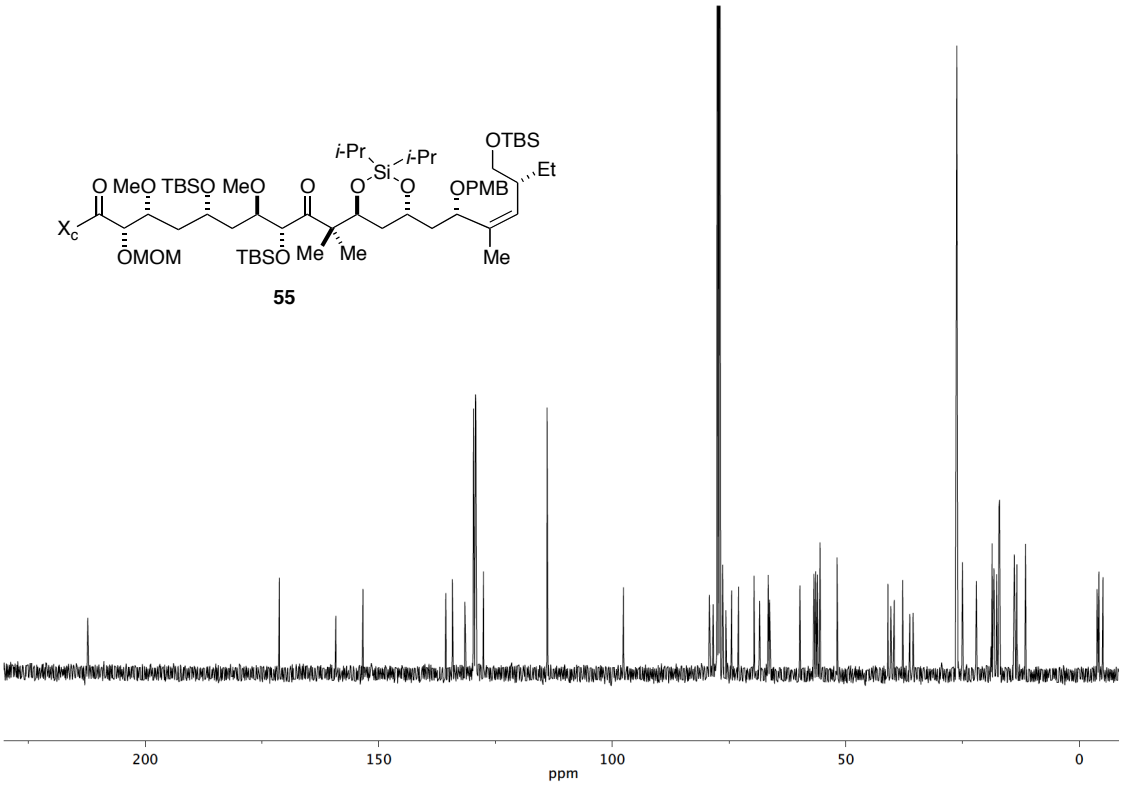

OTBS
Et
O MeO TBSO MeO O OTESO OH
HO 1
11
13
15
OMOM
TBSO Me Me
Me
65
200
150
100
50
0
ppm


Me
O
OMe
TBSO
15
O
1
OTBS
Et
MOMO
TESO
O
O
9
OMe
66
Me Me
OTBS
8
7
6
5
4
3
2
1
0
ppm

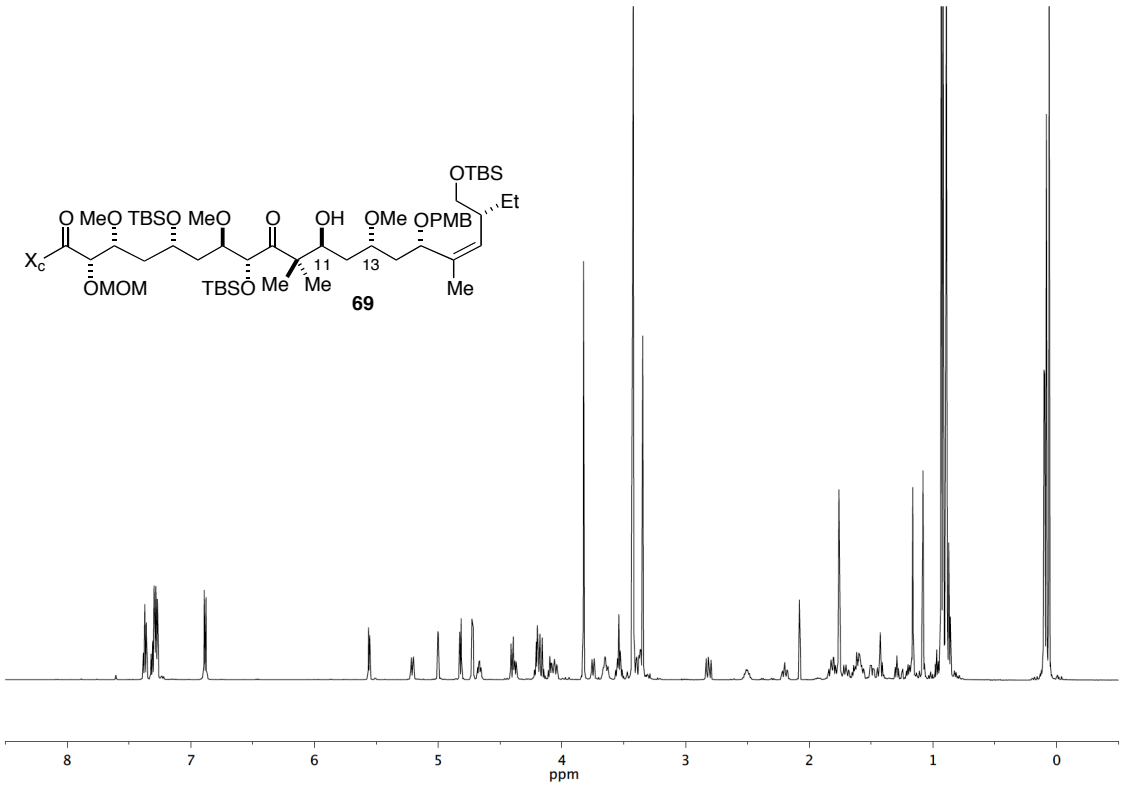

Me
O
OMe
TBSO
15
O
1
OTBS
Et
MOMO
TESO
O
O
9
OMe
66
Me Me
OTBS
200
150
100
50
0
ppm

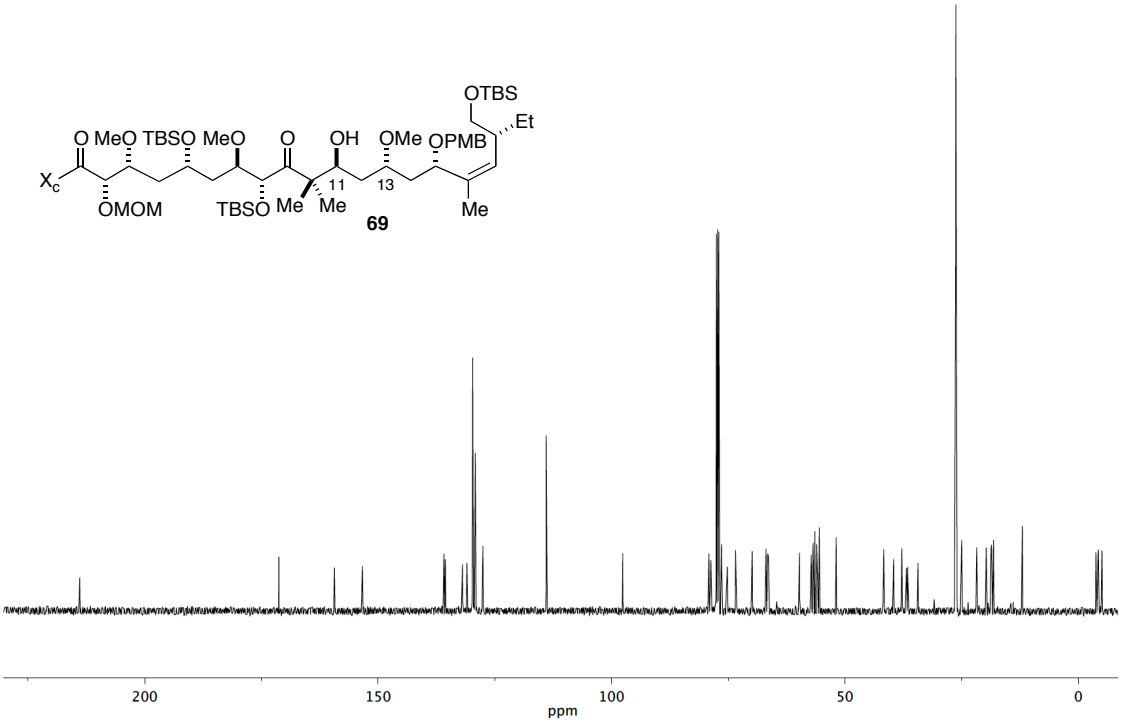

i-Pr
i-Pr
Si
OTBS
Et
O MeO TBSO MeO
O
O
O
OPMB
Xc
OMOM
TBSO
Me
Me
Me
8
7
6
5
4
3
2
1
0
ppm

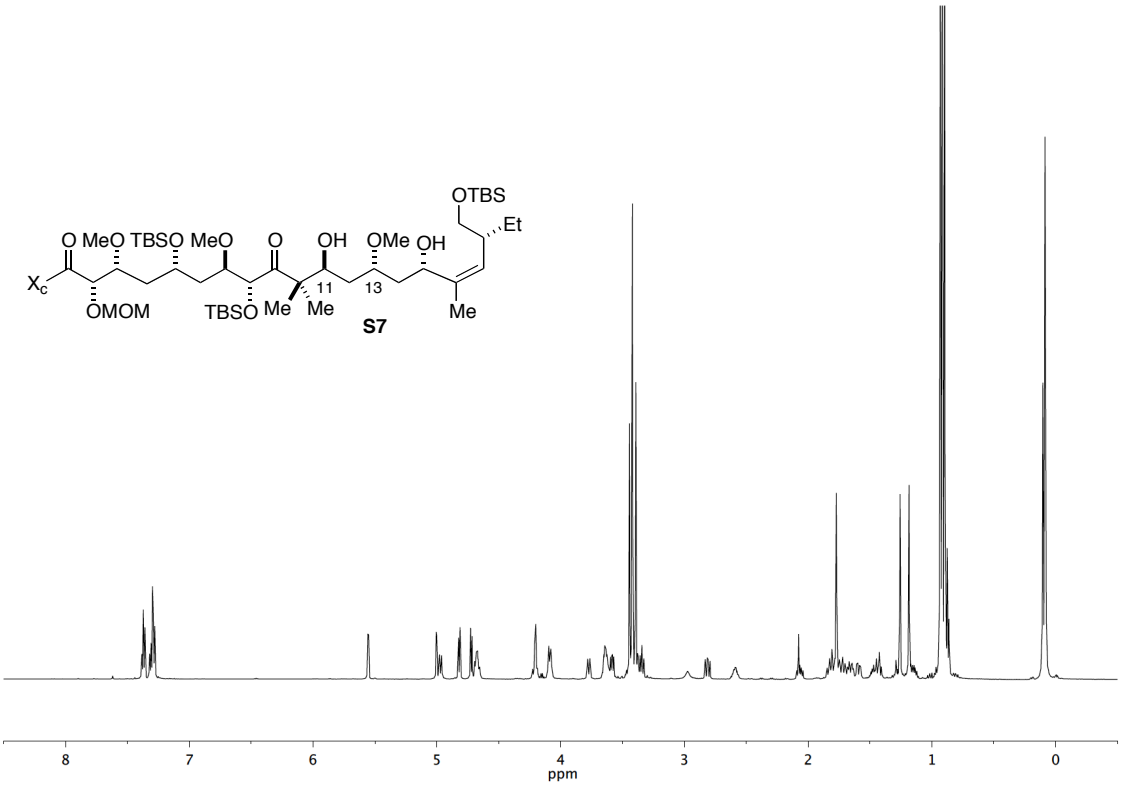
**55**

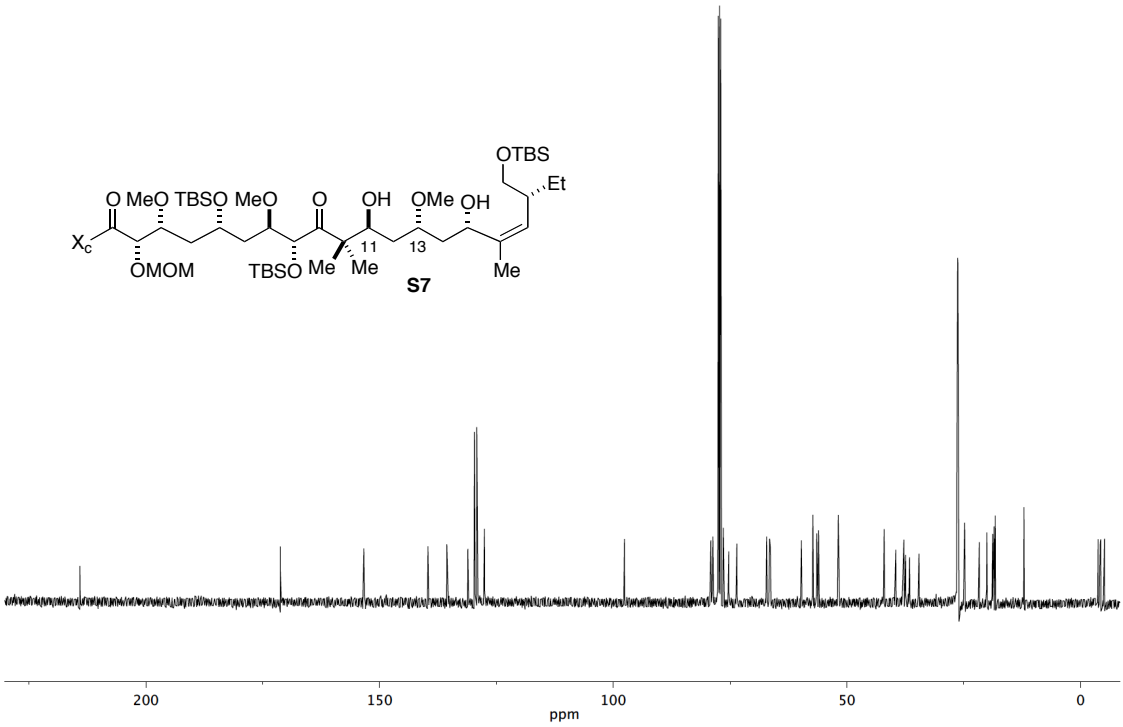

i-Pr
i-Pr
Si
OTBS
Et
O MeO TBSO MeO
O
O
O
OPMB
Xc
OMOM
TBSO
Me
Me
Me
200
150
100
50
0
ppm

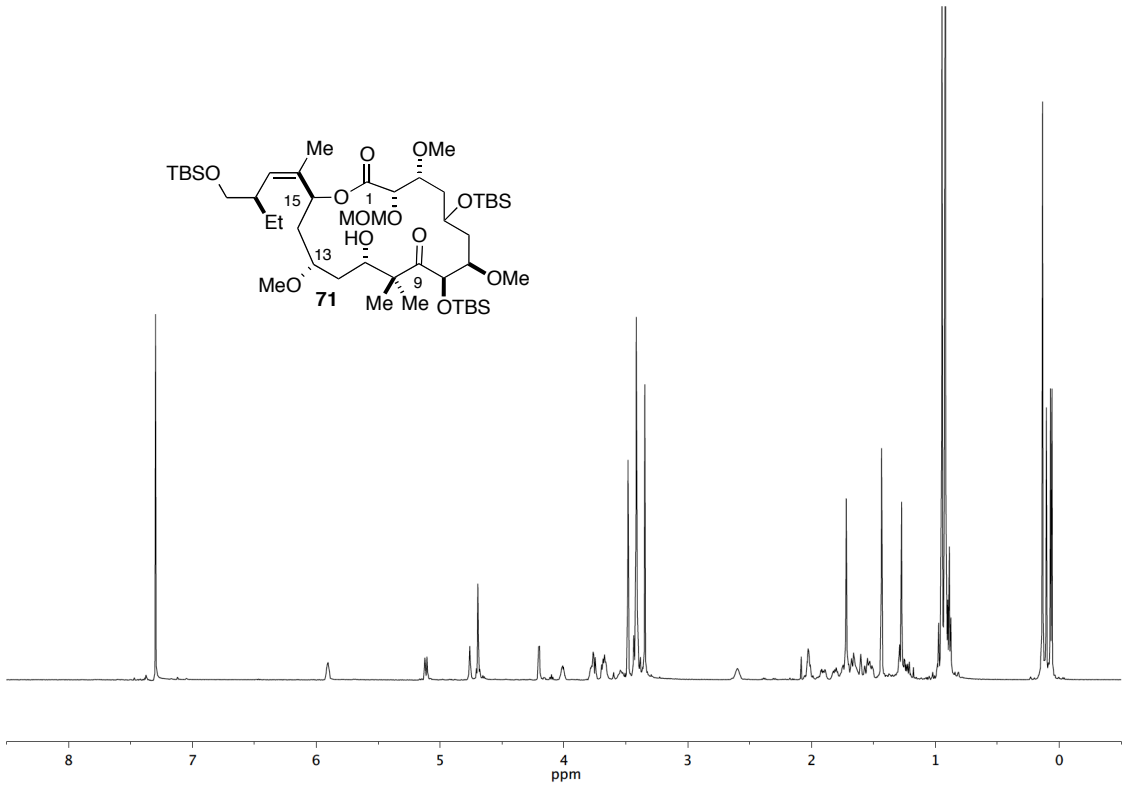
**55**

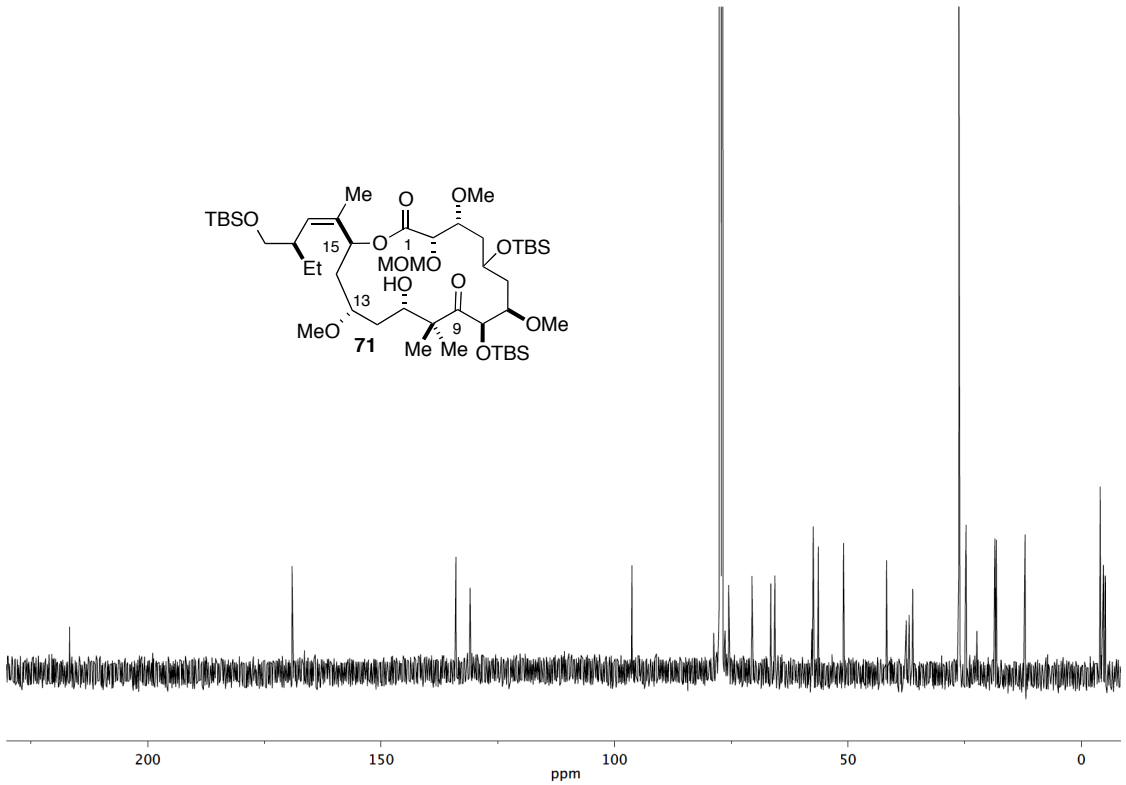

OTBS
Et
O MeO TBSO MeO O OH OMe OPMB
Xc
11
13
OMOM
TBSO Me Me
Me
69
8
7
6
5
4
3
2
1
0
ppm

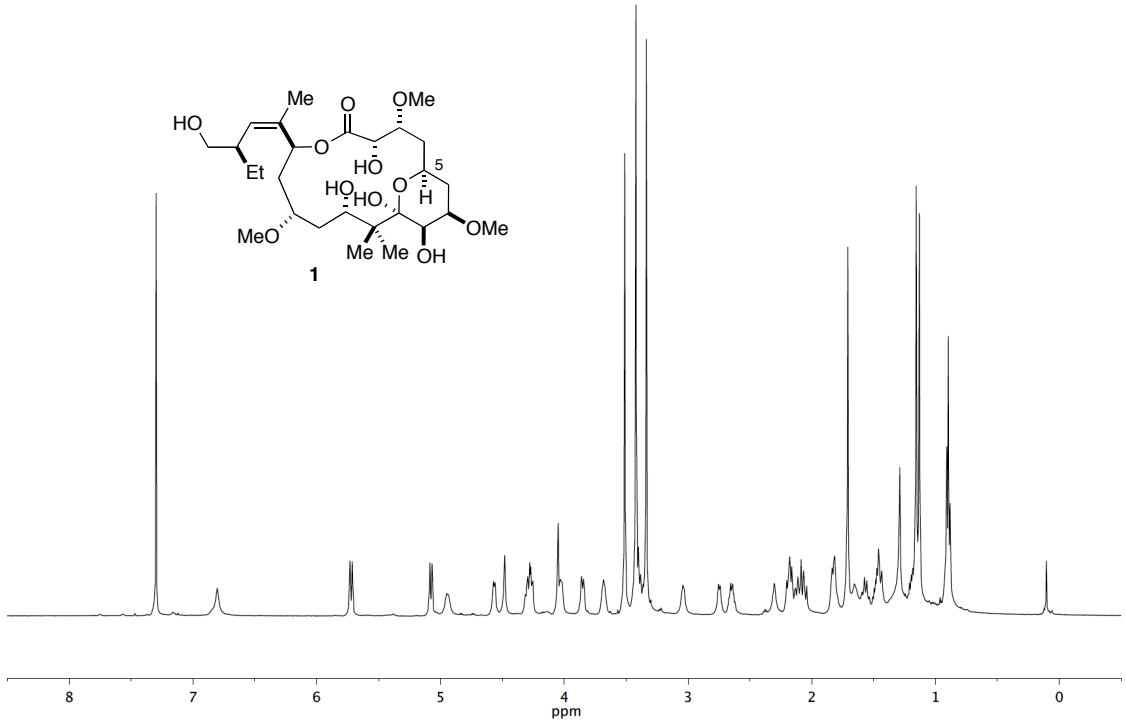

OTBS
Et
O MeO TBSO MeO O OH OMe OPMB
Xc
11
13
OMOM
TBSO Me Me
Me
69
200
150
100
50
0
ppm

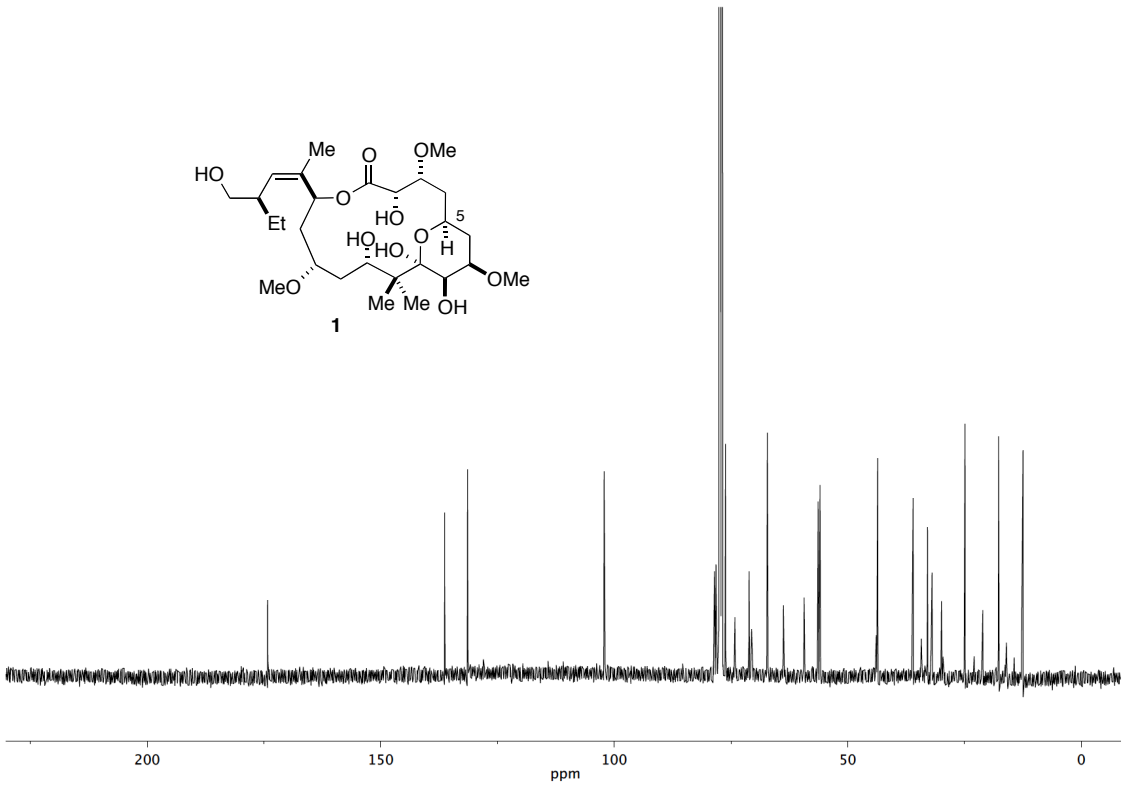

OTBS
Et
O MeO TBSO MeO O OH OMe OH
Xc
11
13
OMOM
TBSO Me Me
Me
S7
8
7
6
5
4
3
2
1
0
ppm


OTBS
Et
O MeO TBSO MeO O OH OMe OH
Xc
11
13
OMOM
TBSO Me Me
Me
S7
200
150
100
50
0
ppm

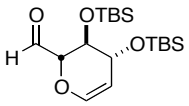

TBSO
Me
O
OMe
15
O
1
OTBS
Et
MOMO
HO
O
13
MeO
9
OMe
71
Me Me
OTBS
8
7
6
5
4
3
2
1
0
ppm


TBSO
Me
O
OMe
15
O
1
OTBS
Et
MOMO
HO
O
13
MeO
9
OMe
71
Me Me
OTBS
200
150
100
50
0
ppm


Me
O
OMe
HO
O
Et
HO
5
HO
HO
O
H
MeO
OMe
Me
Me
OH
1
8
7
6
5
4
3
2
1
0
ppm

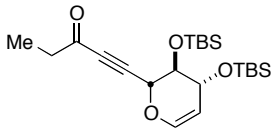

Me
O
OMe
HO
O
Et
HO
5
HO
HO
O
H
MeO
OMe
Me
Me
OH
1
200
150
100
50
0
ppm

# II. NMR Spectra From Chapter 4

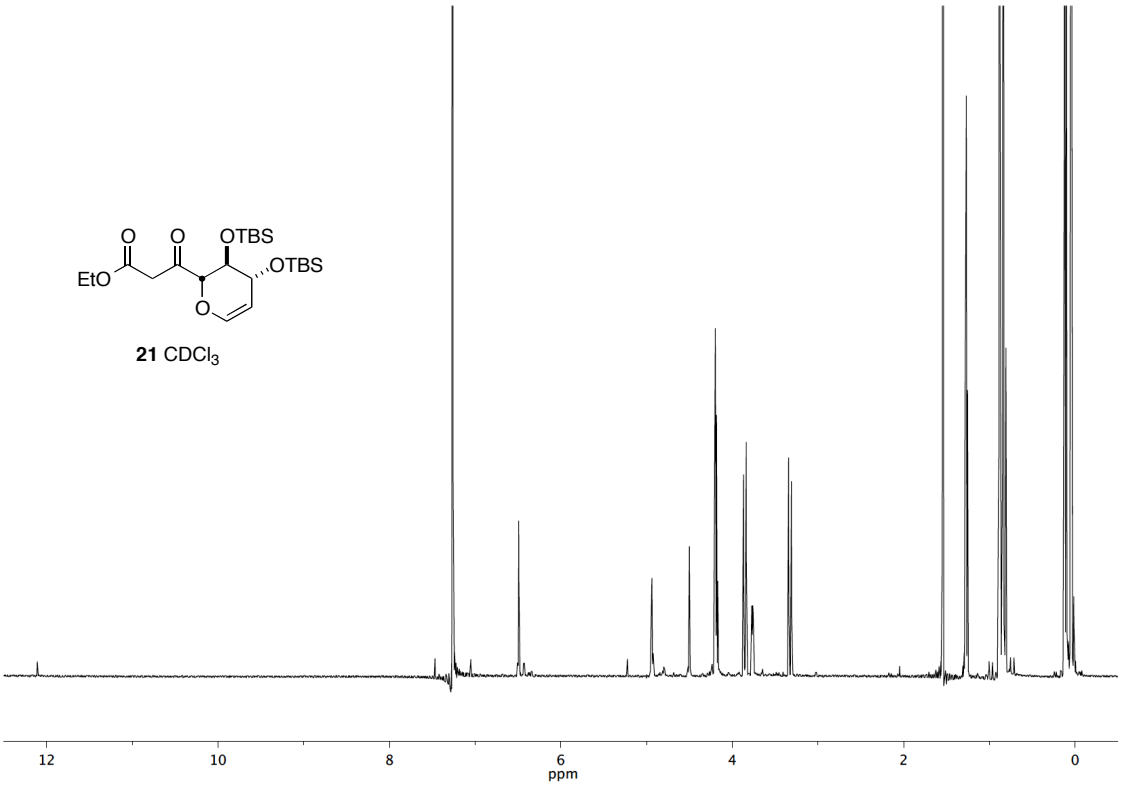



**20** $CDCl_3$

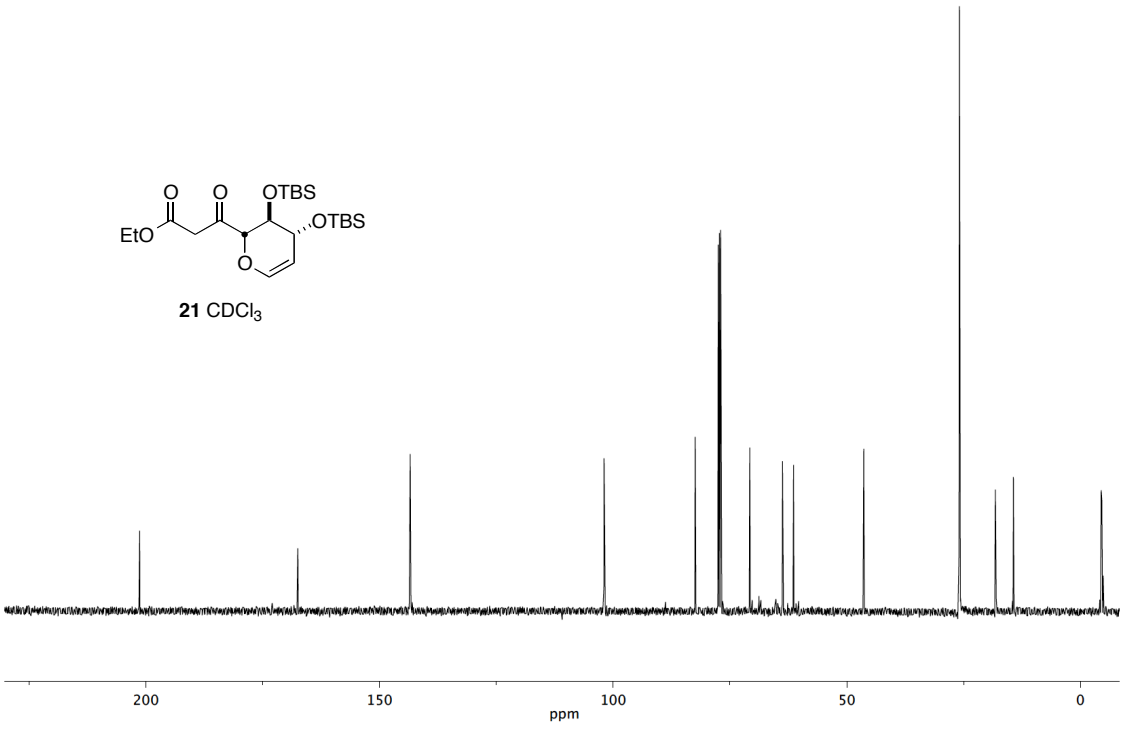


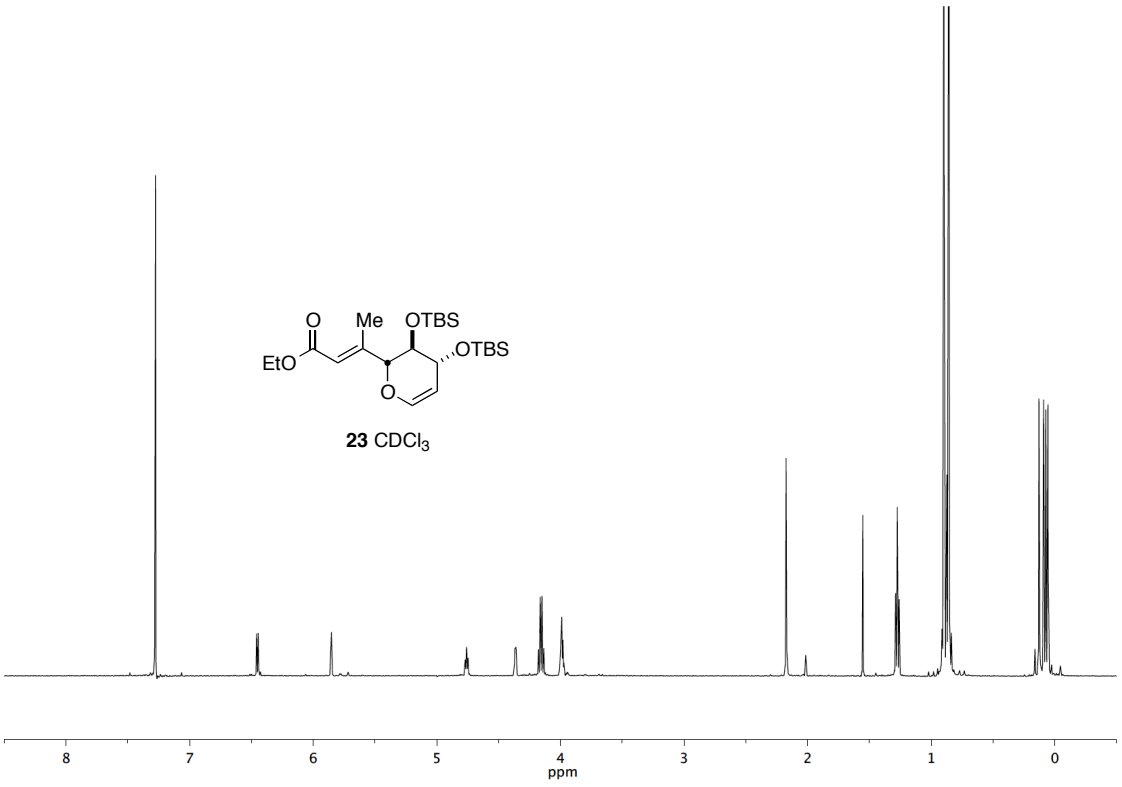

**10** $CDCl_3$



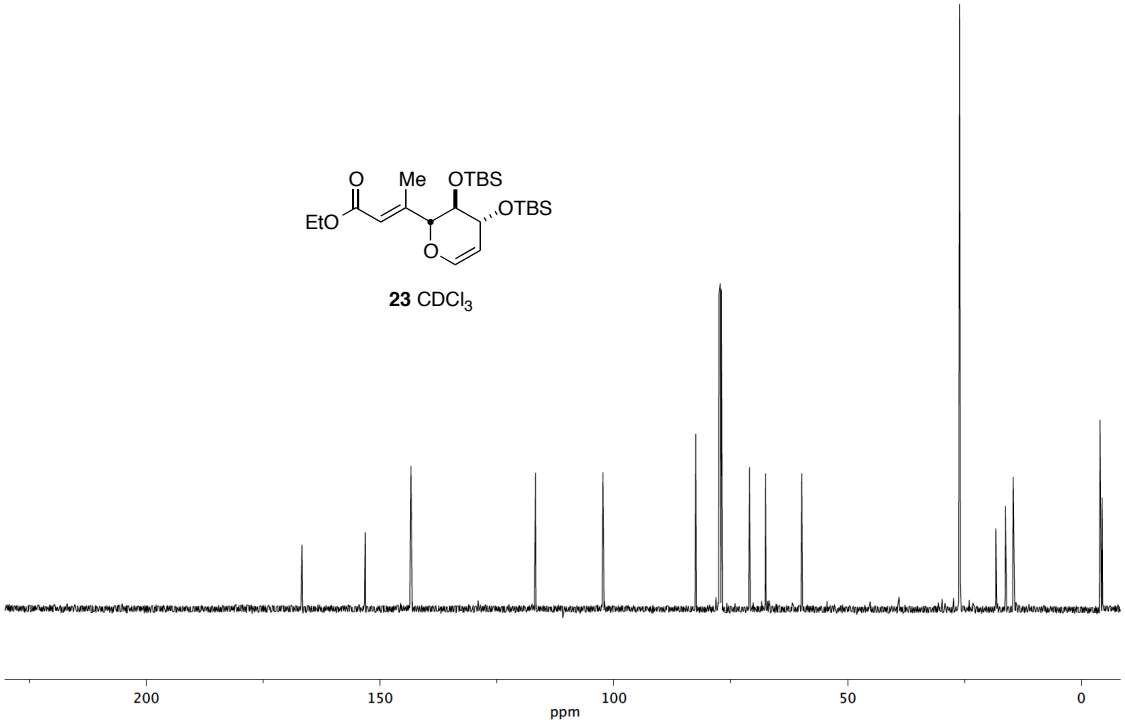

**21** $CDCl_3$



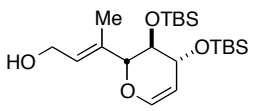

**21** $CDCl_3$




**23** $CDCl_3$

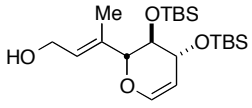



**23** $CDCl_3$

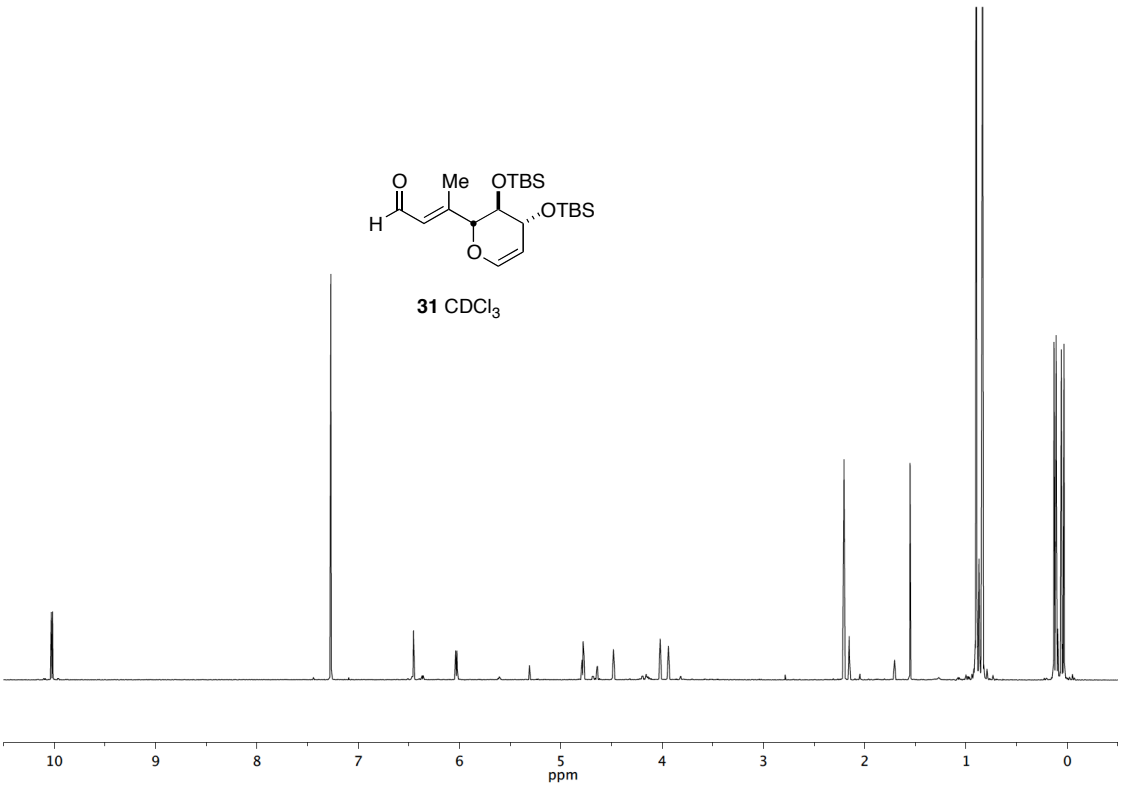



**30** $CDCl_3$

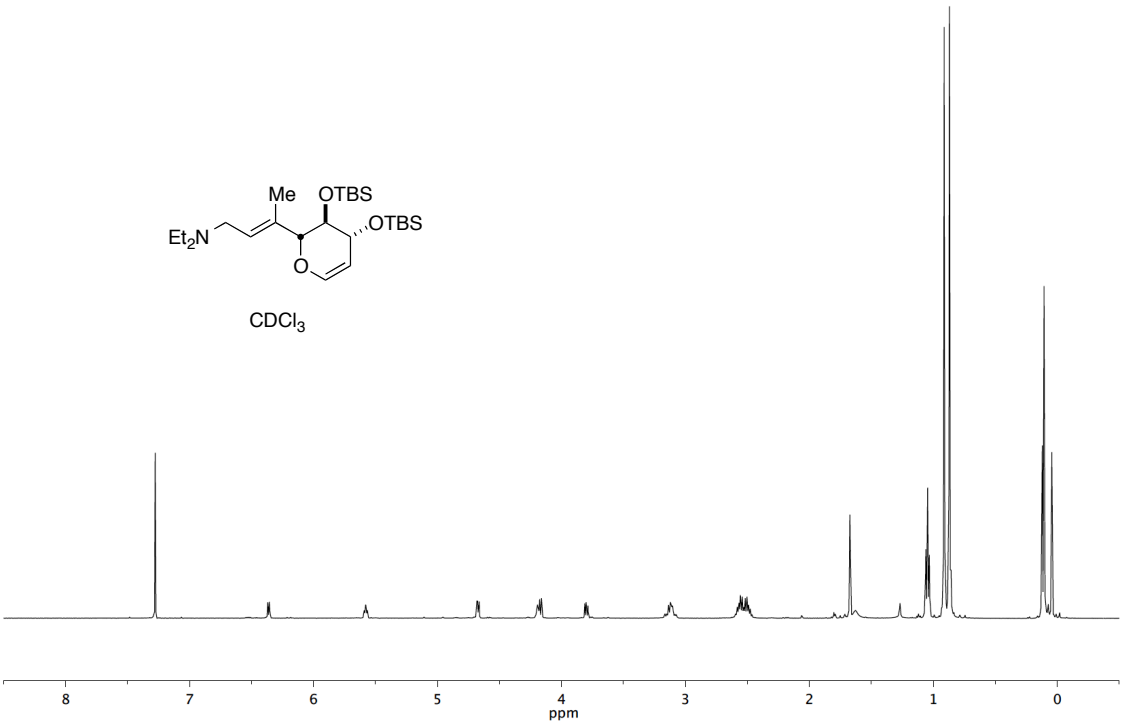


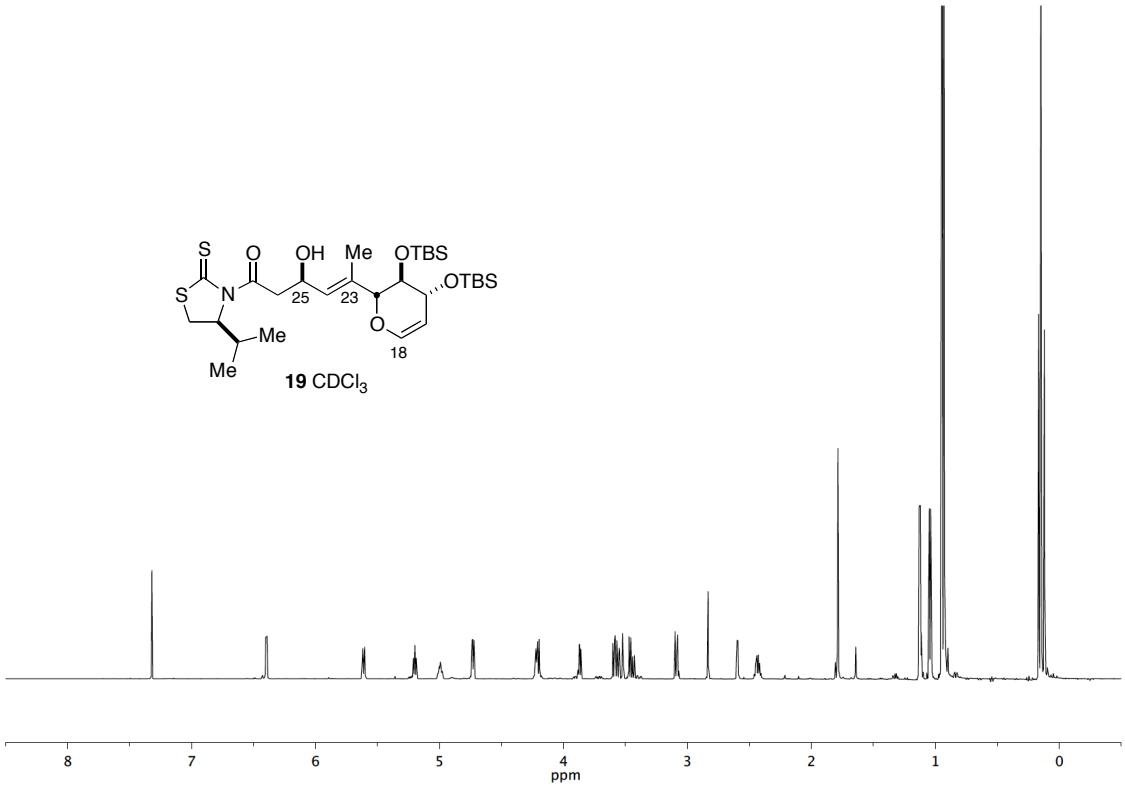

**30** $CDCl_3$



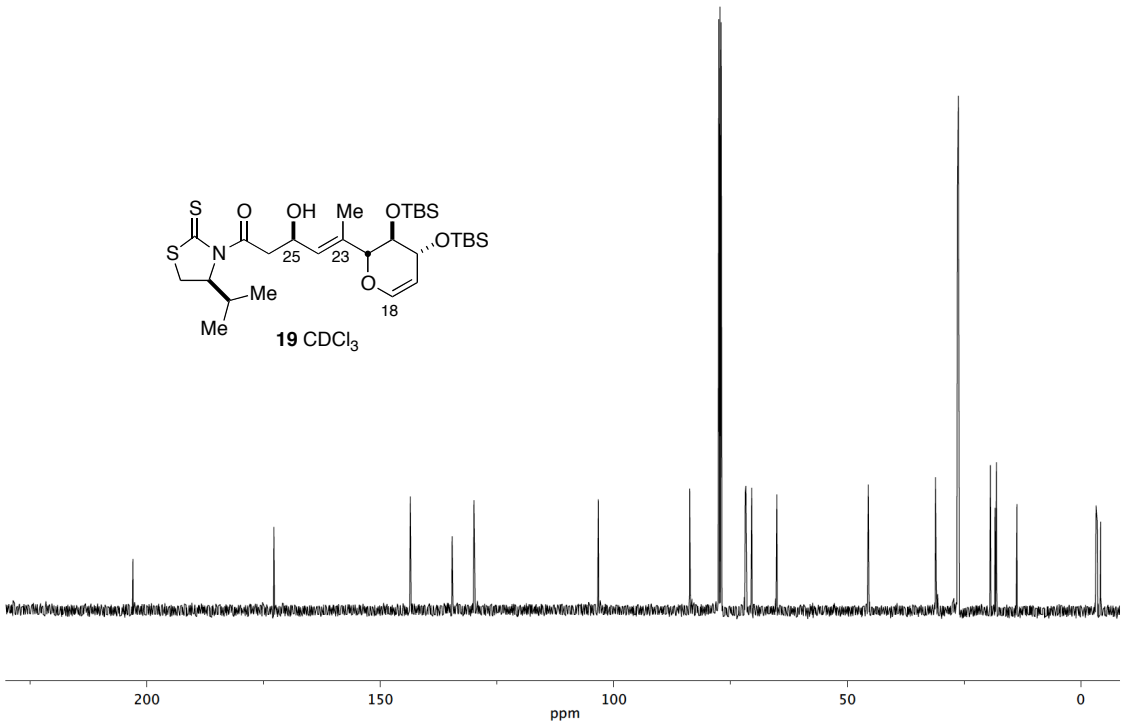

**31** $CDCl_3$



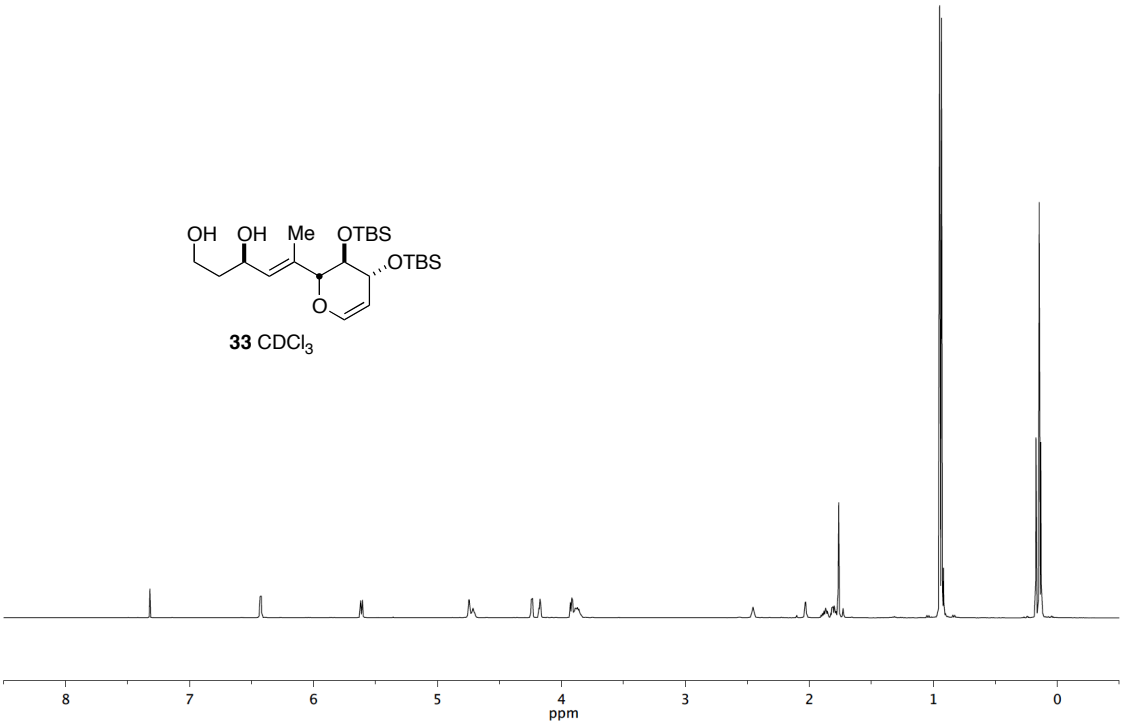

$CDCl_3$



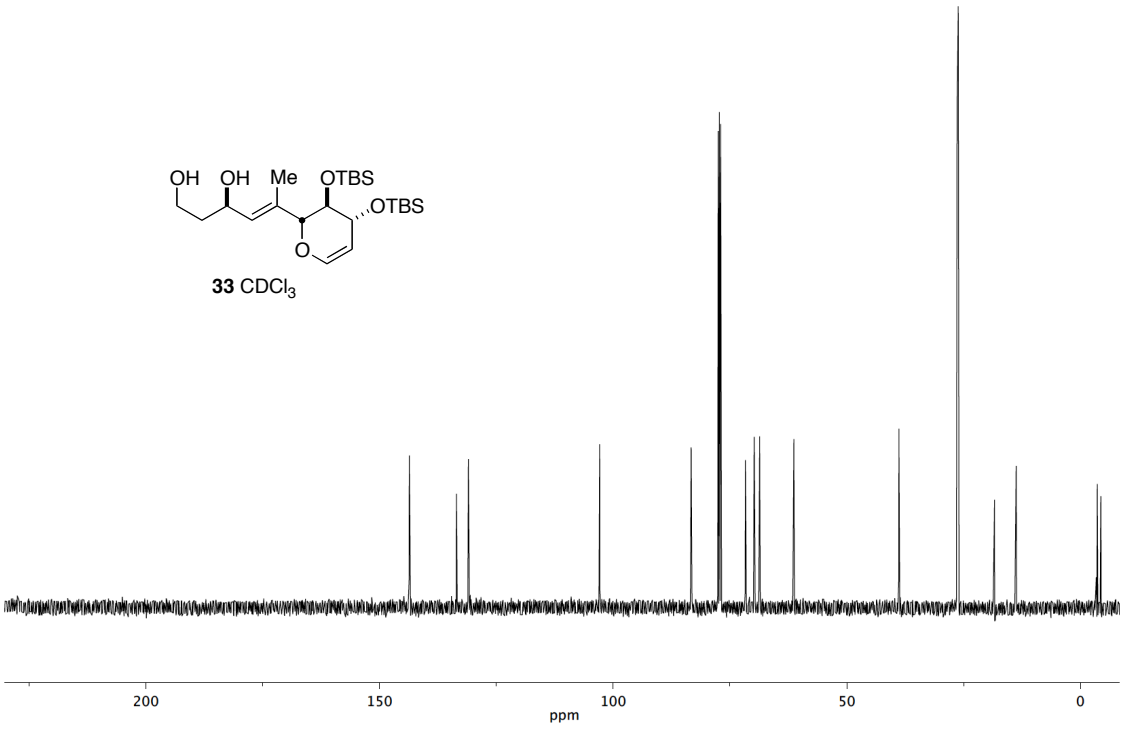

**19** $CDCl_3$



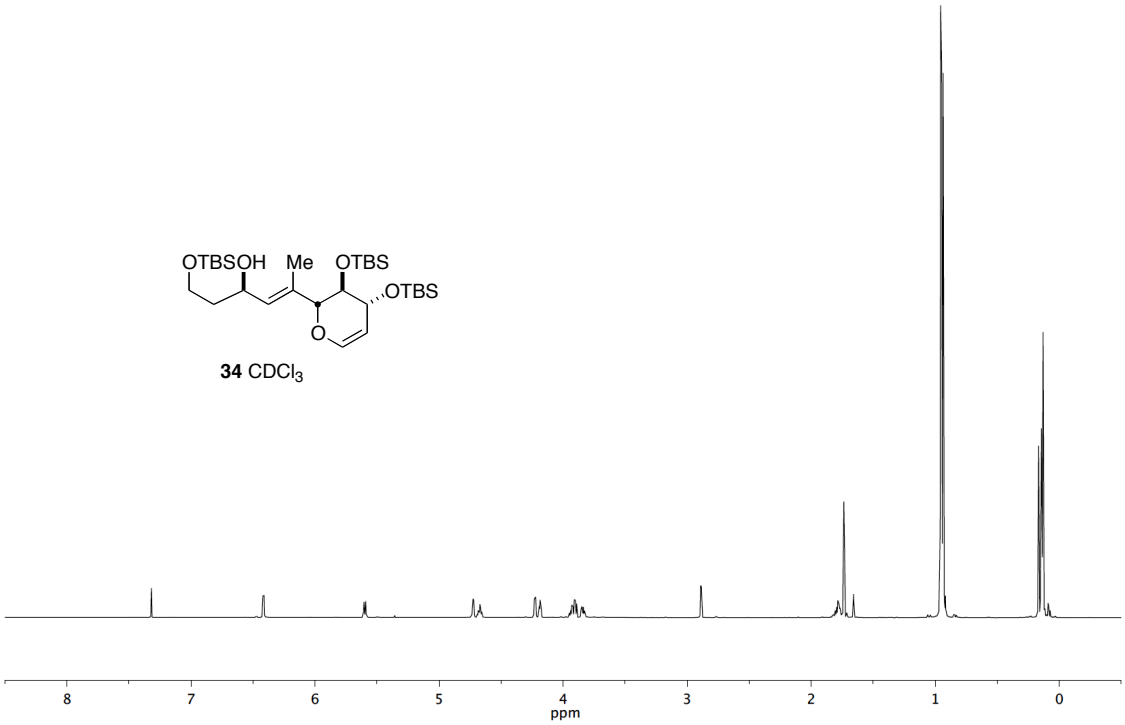

**19** $CDCl_3$



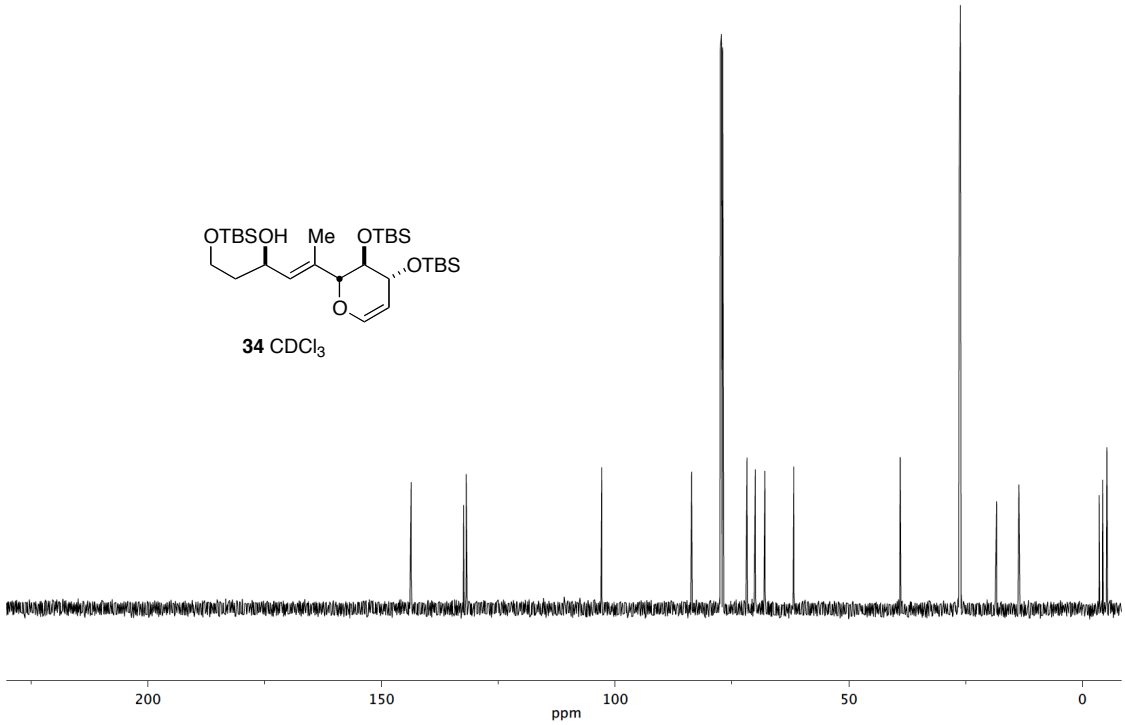

**33** $CDCl_3$



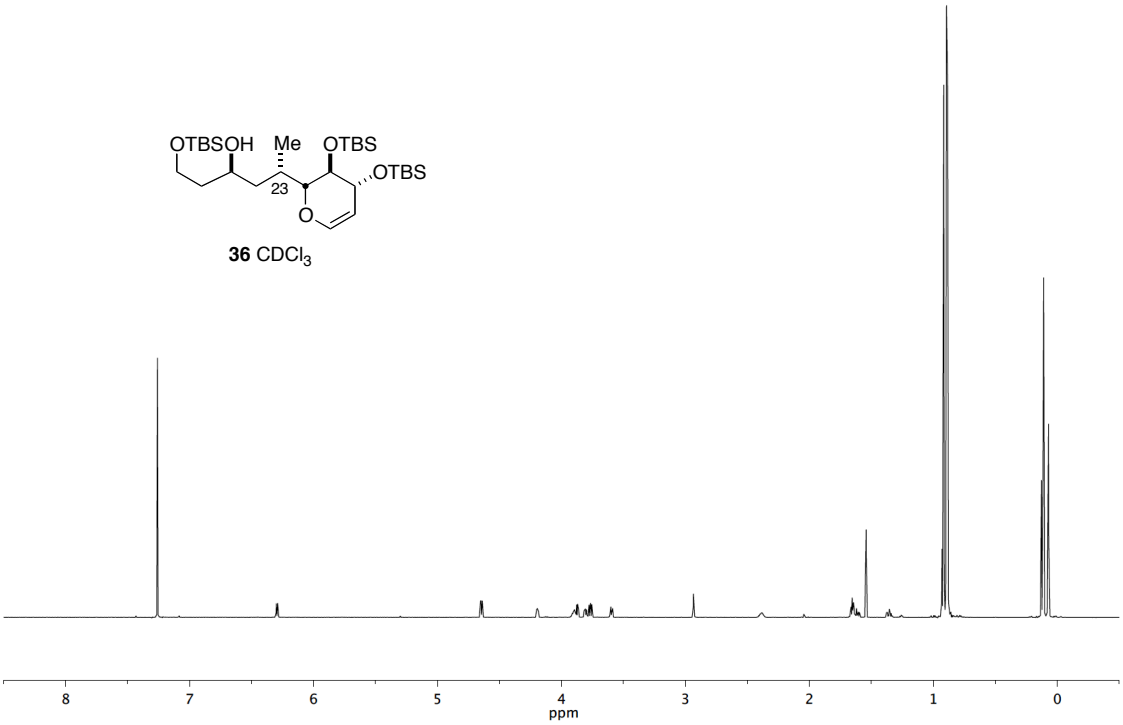

**33** $CDCl_3$



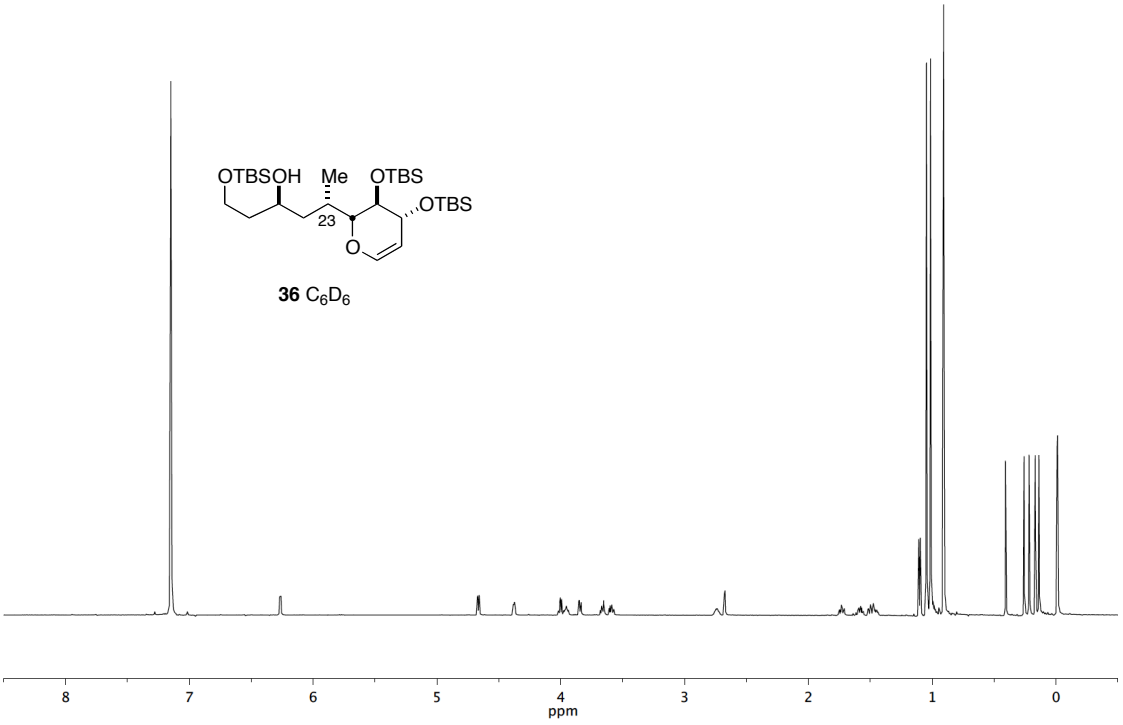

**34** $CDCl_3$



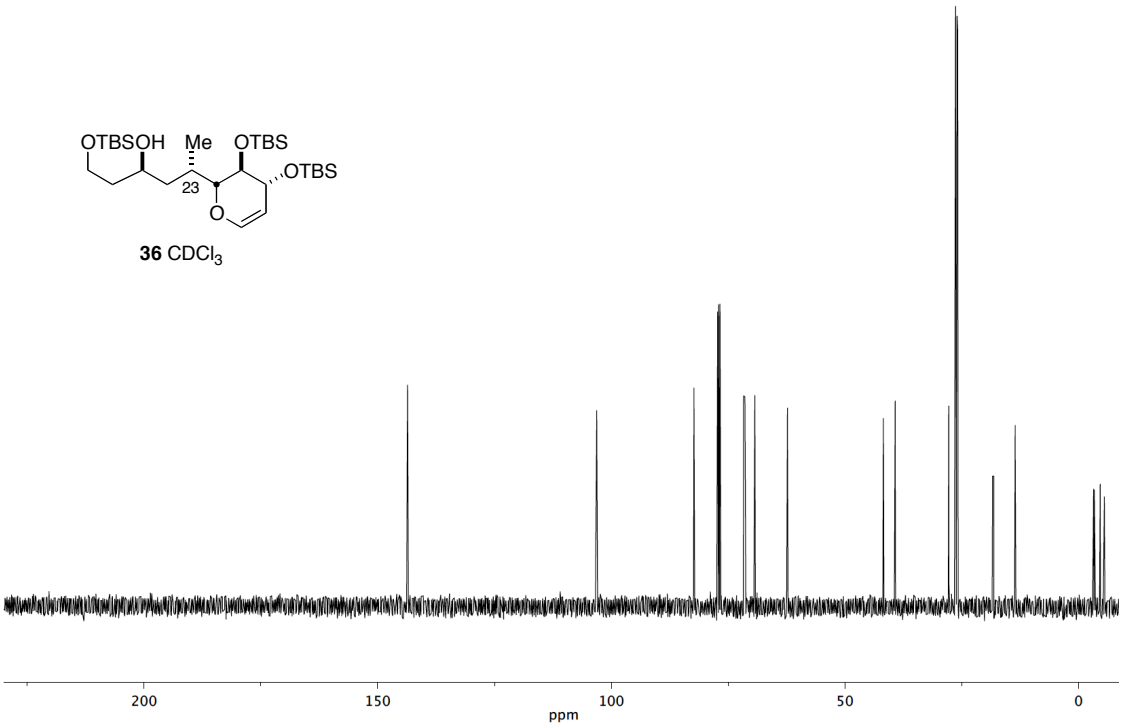

**34** $CDCl_3$



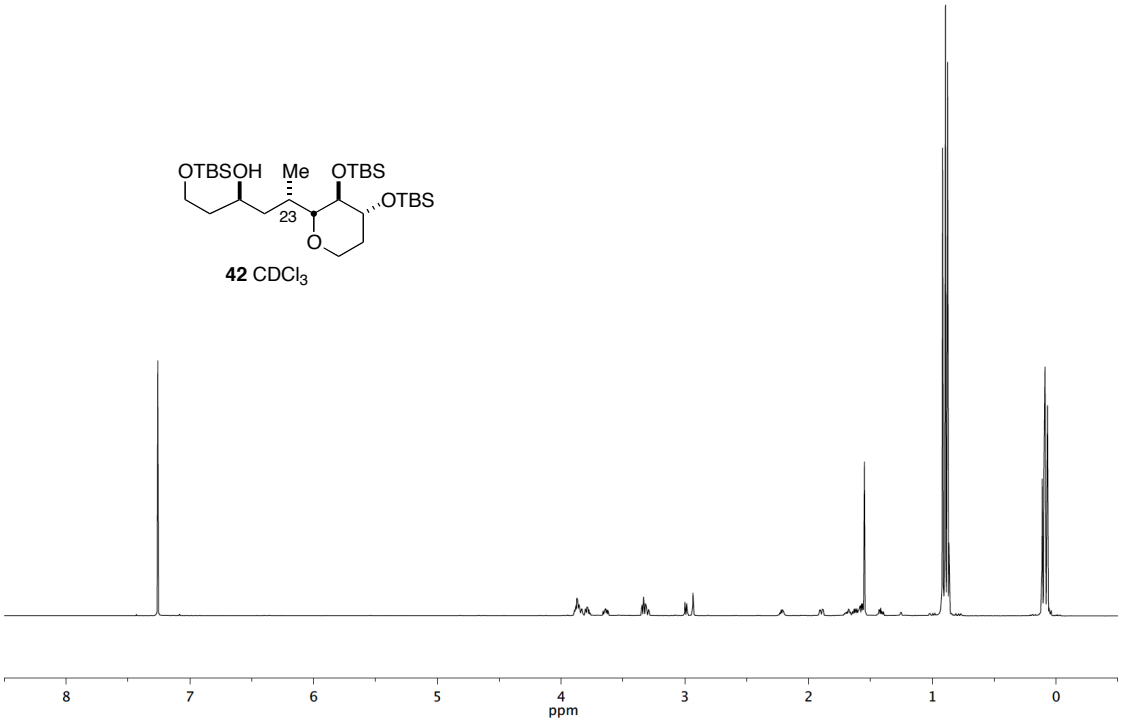

**36** $CDCl_3$



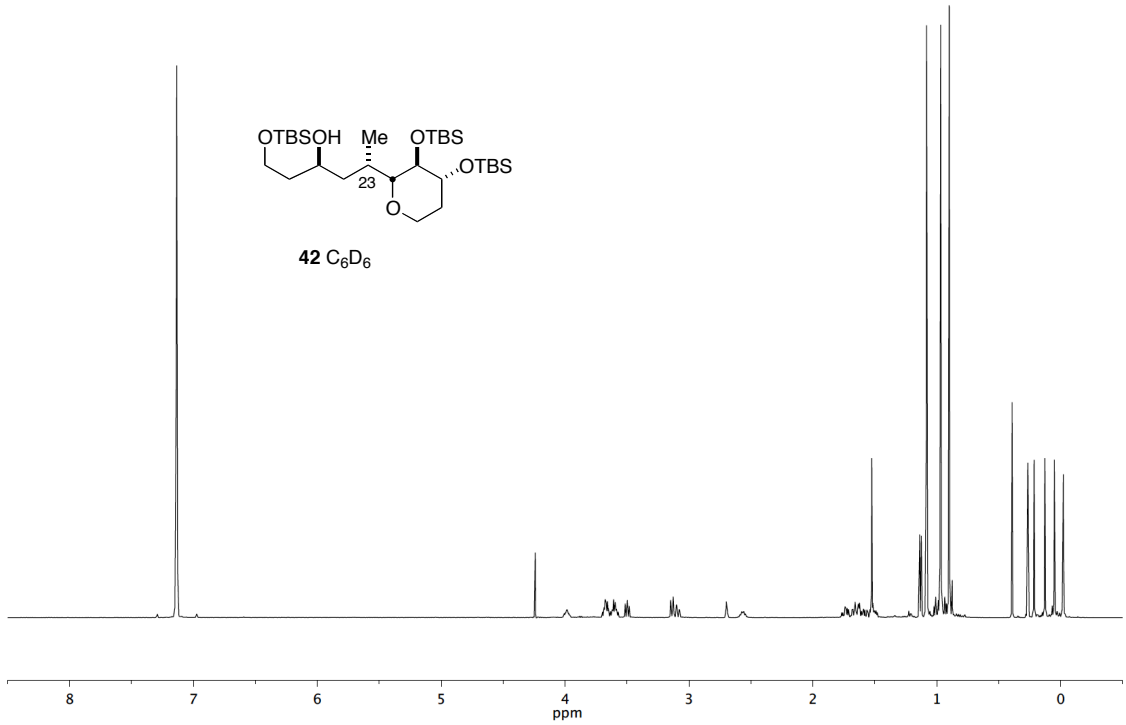

**36** $C_6D_6$



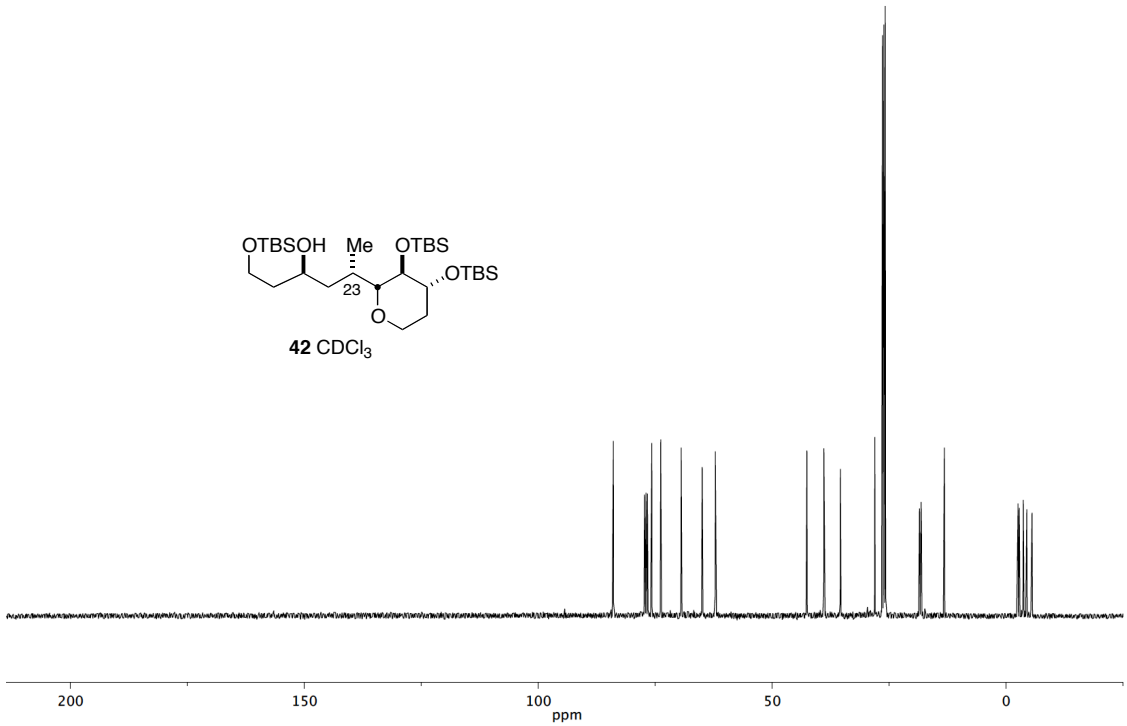

**36** $CDCl_3$



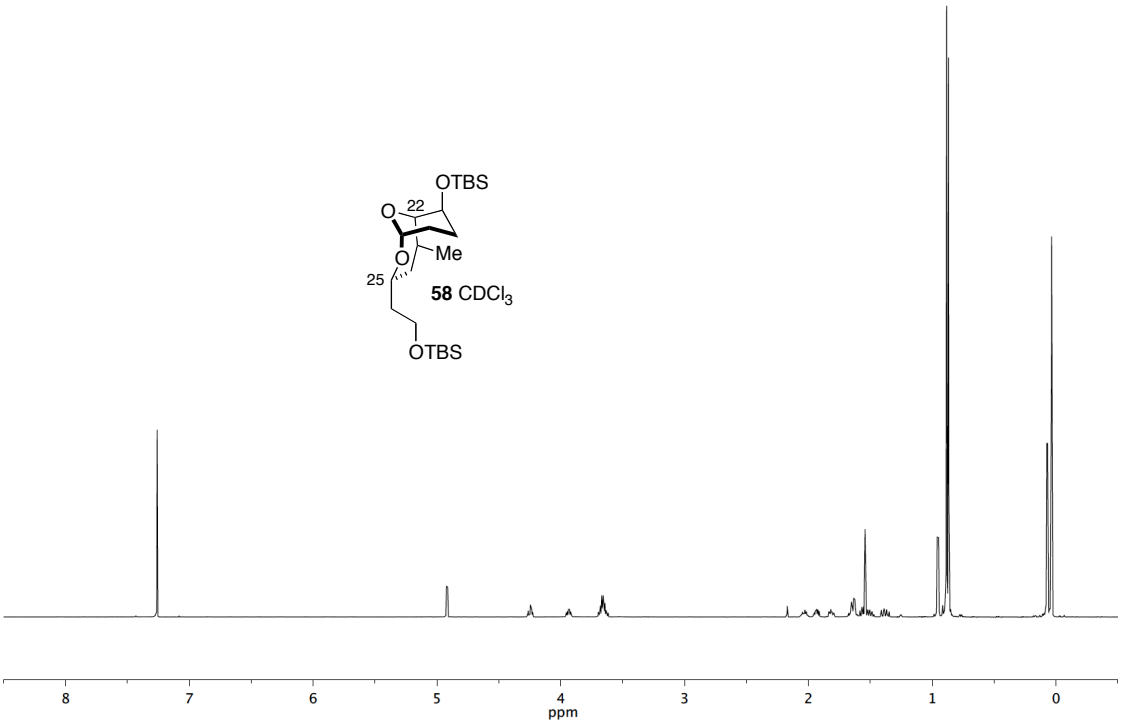

**42** $CDCl_3$

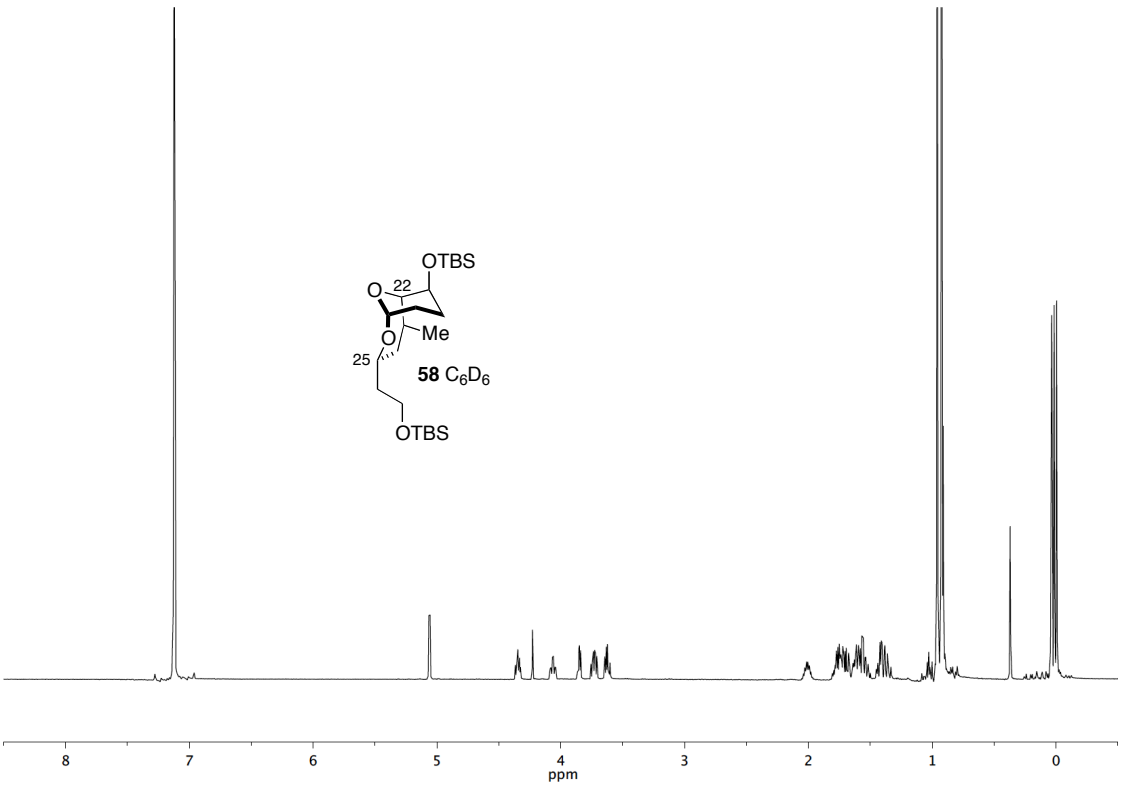


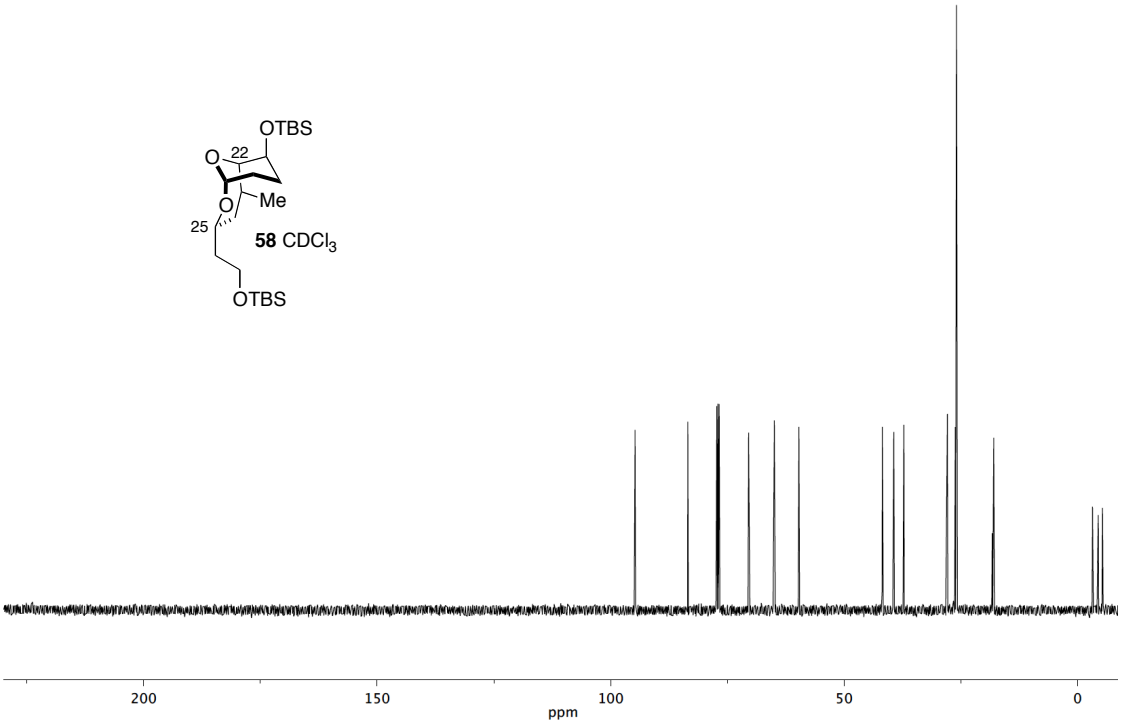

**42** $C_6D_6$



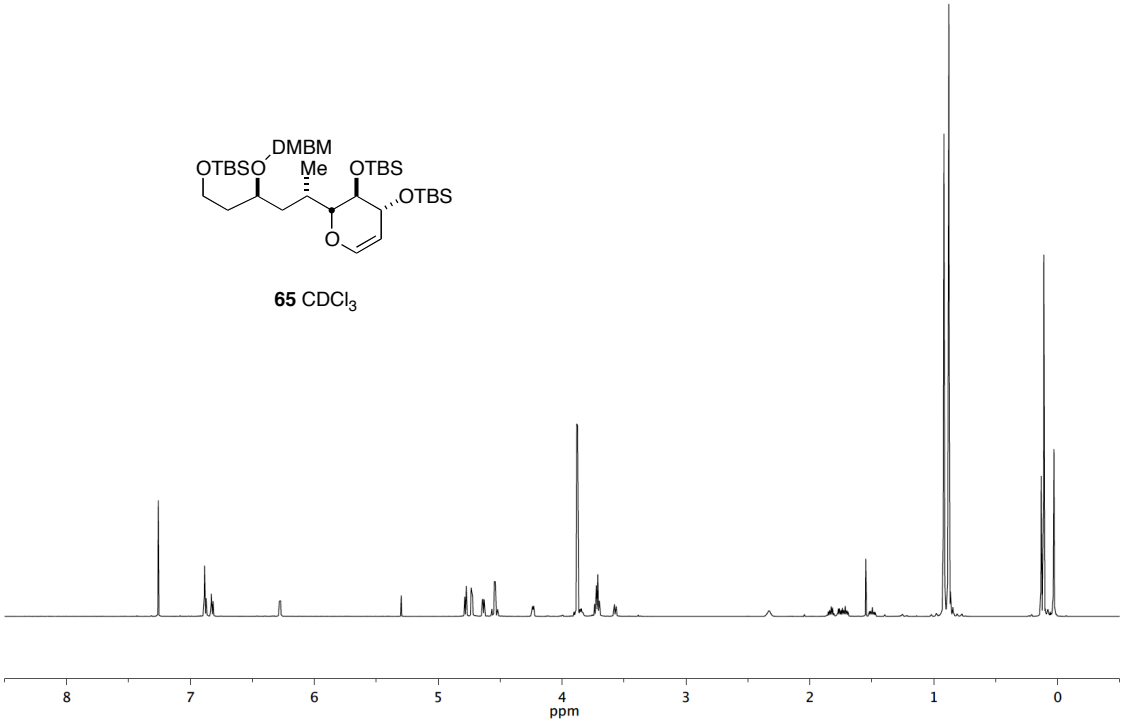

**42** $CDCl_3$


OTBS
O
22
O
Me
25
58 CDCl3
OTBS
8
7
6
5
4
3
2
1
0
ppm

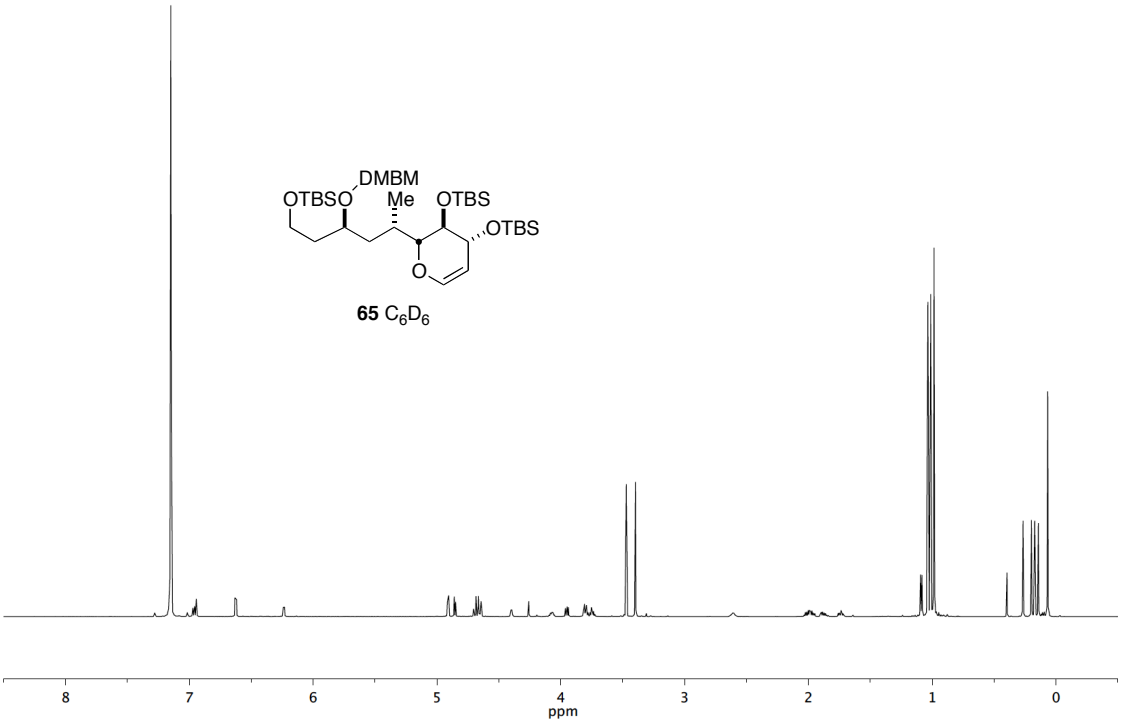

OTBS
O
22
O
Me
25
58 C6D6
OTBS
8
7
6
5
4
3
2
1
0
ppm



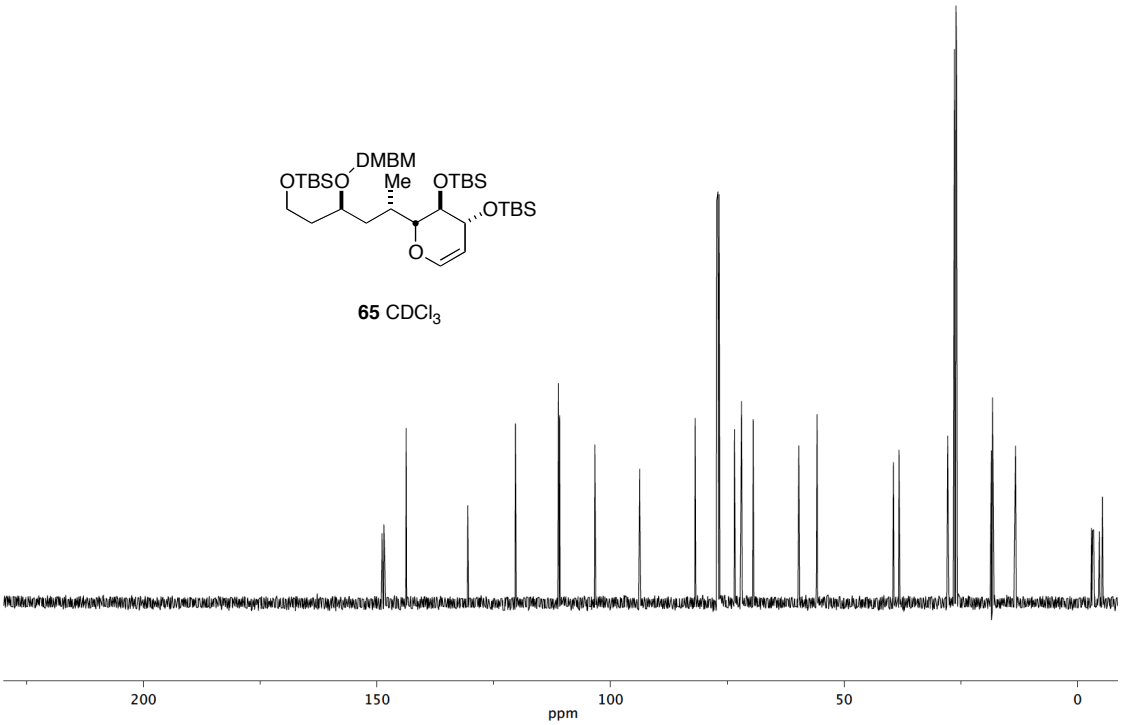

**58** $CDCl_3$



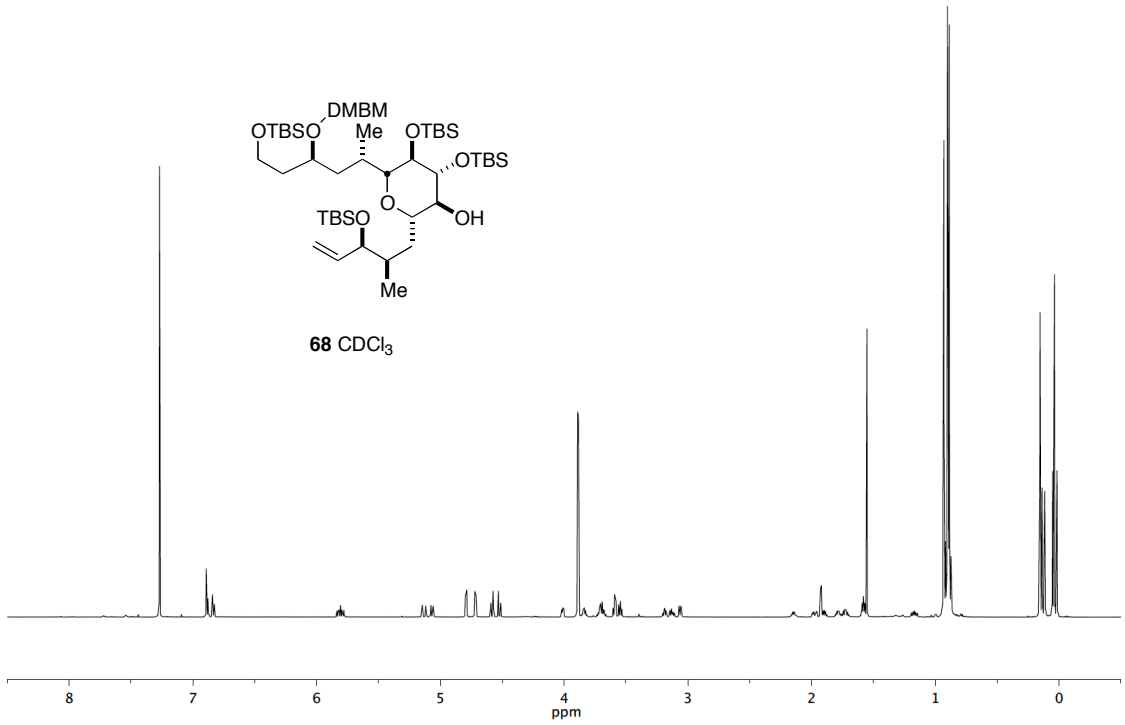

**65** $CDCl_3$



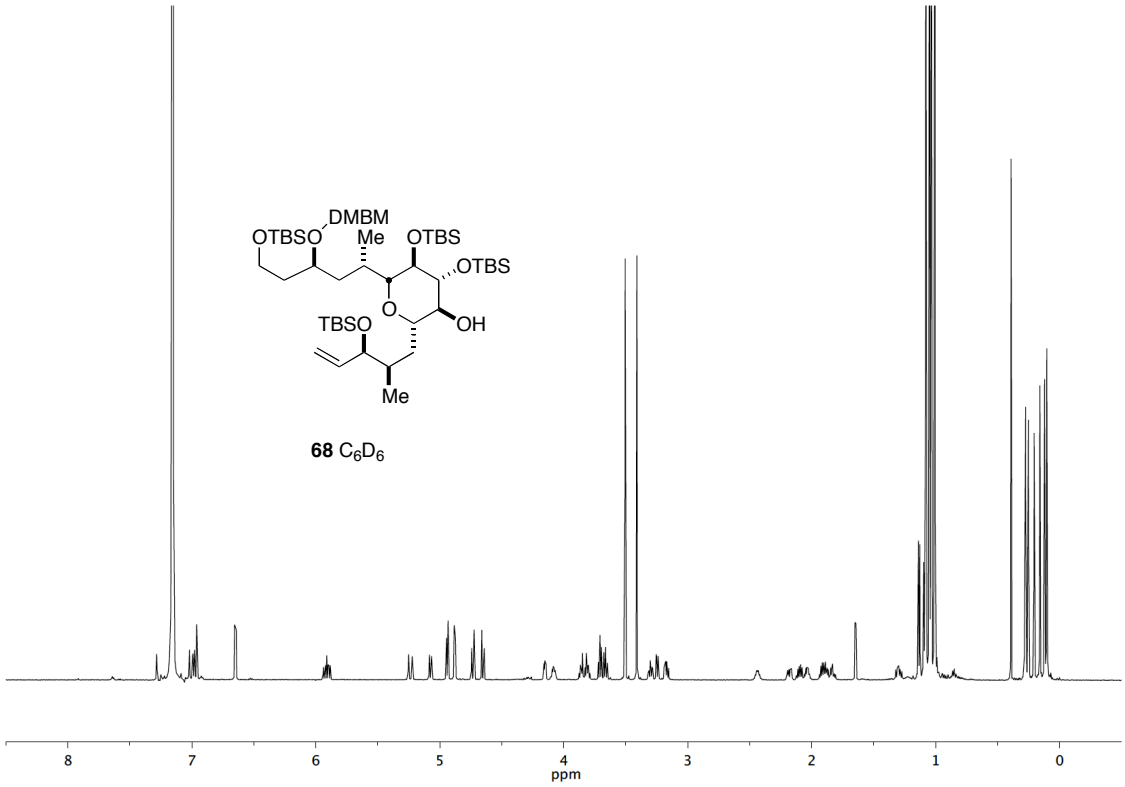

**65** $C_6D_6$



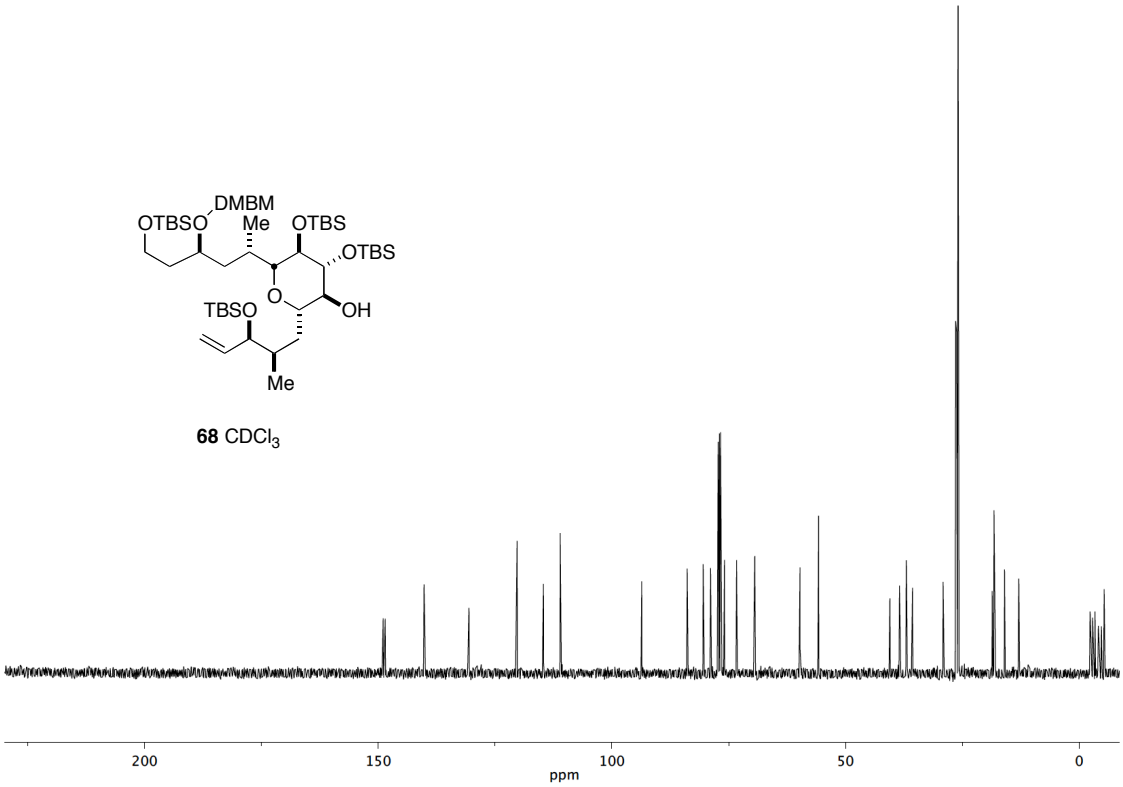

**65** $CDCl_3$



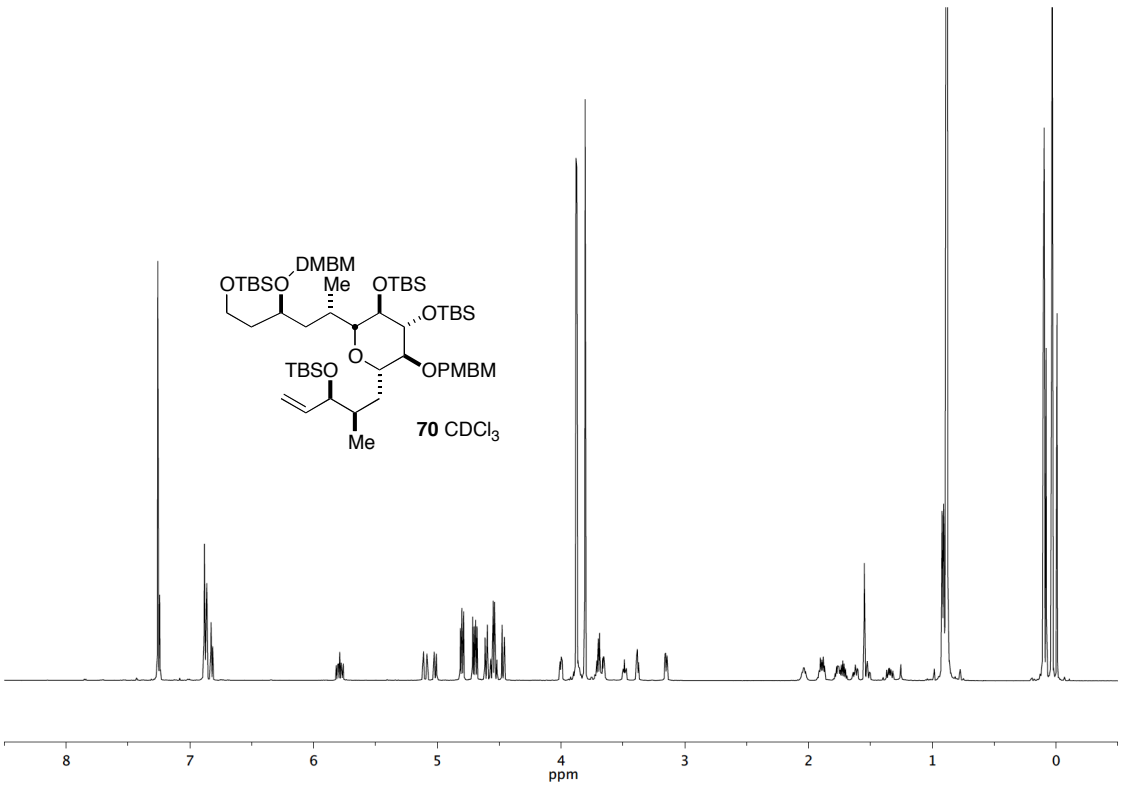

**68** $CDCl_3$



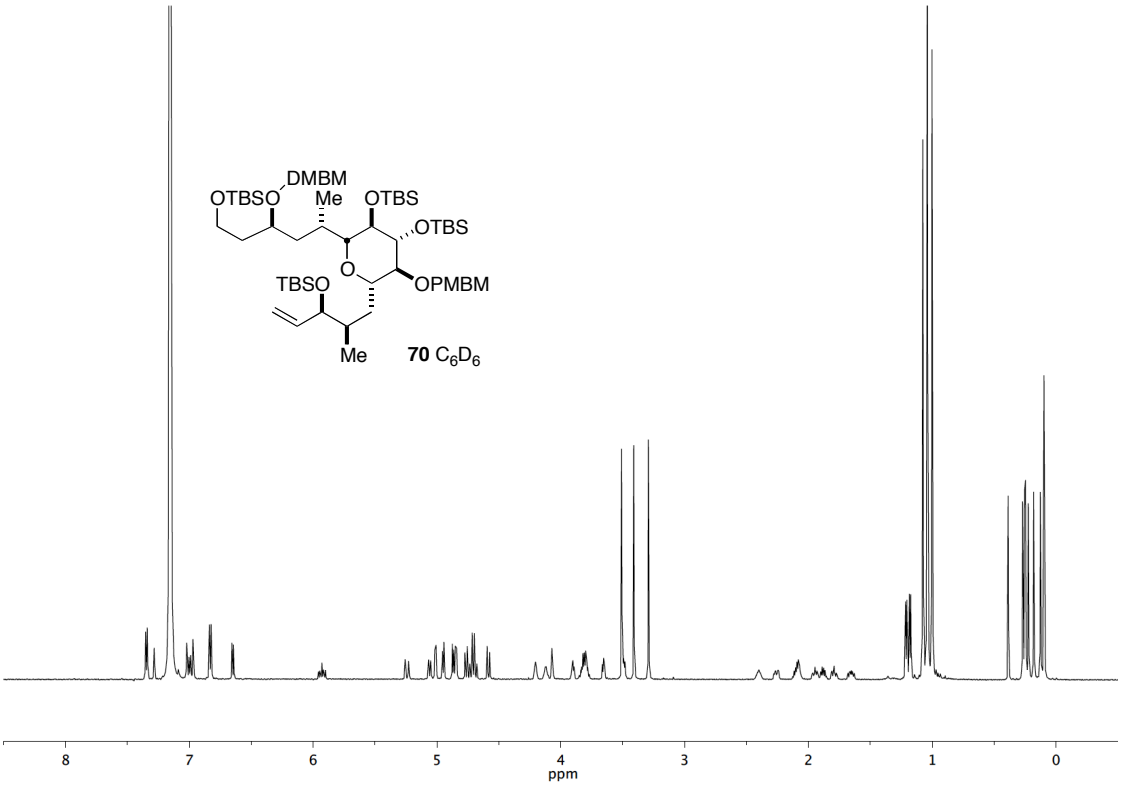

**68** $C_6D_6$

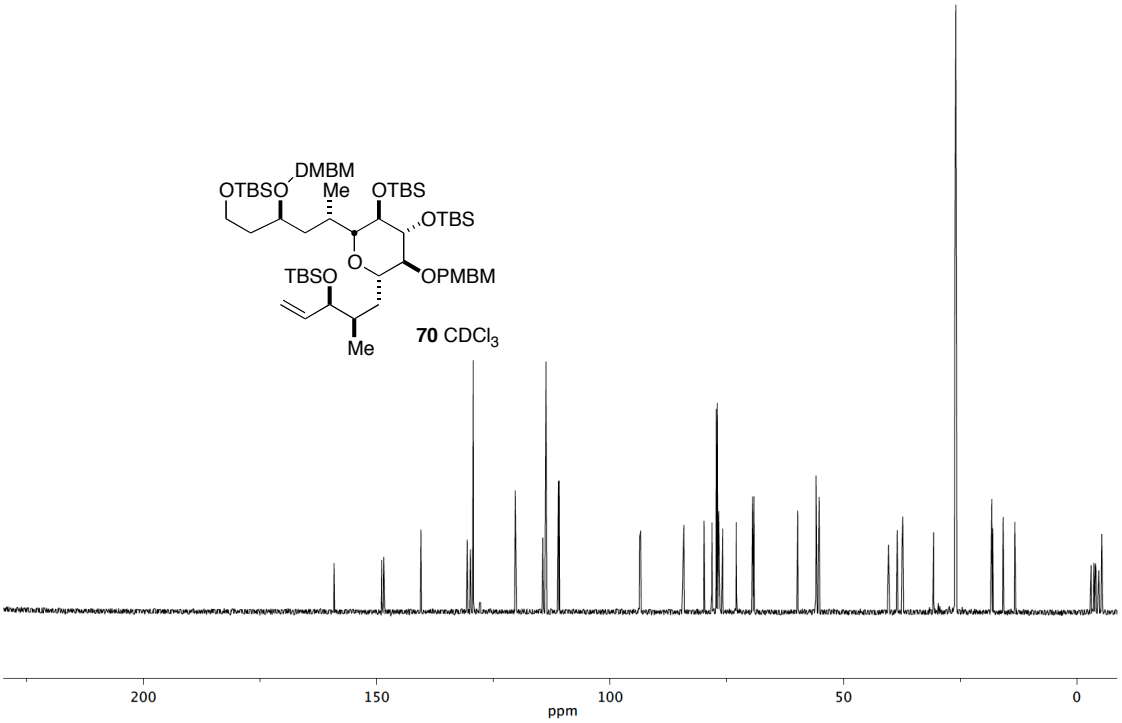


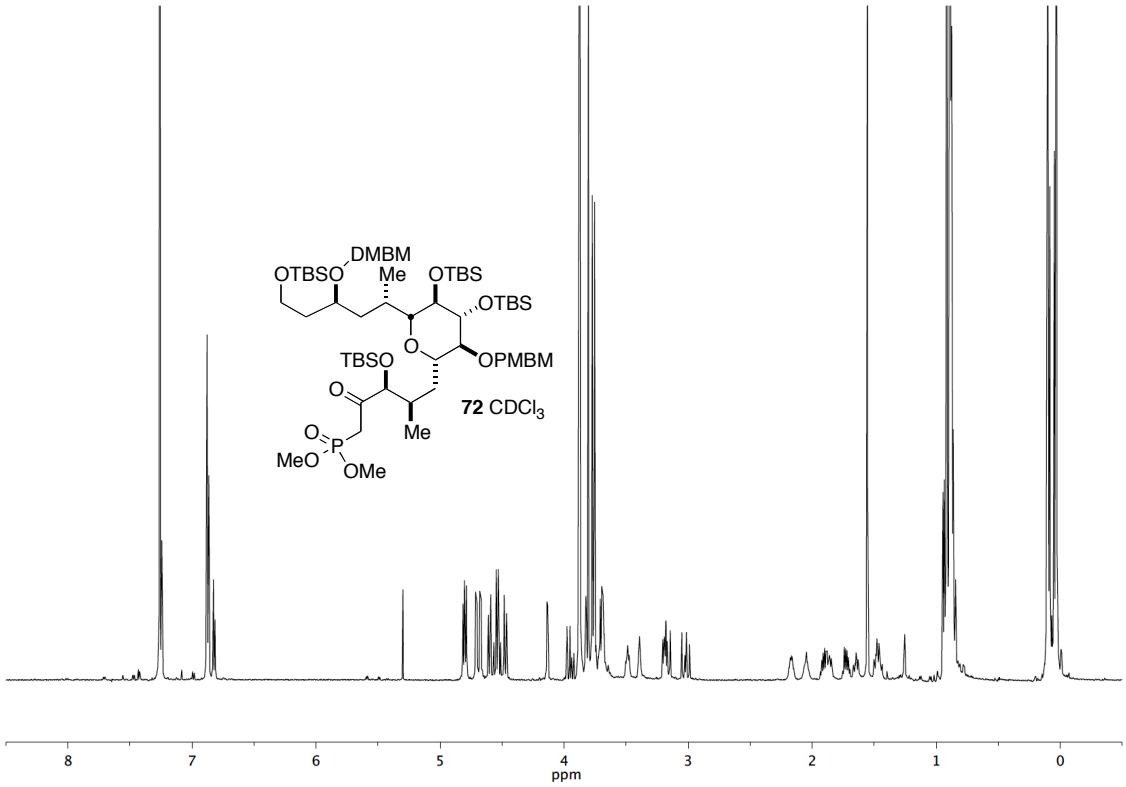

**68** $CDCl_3$

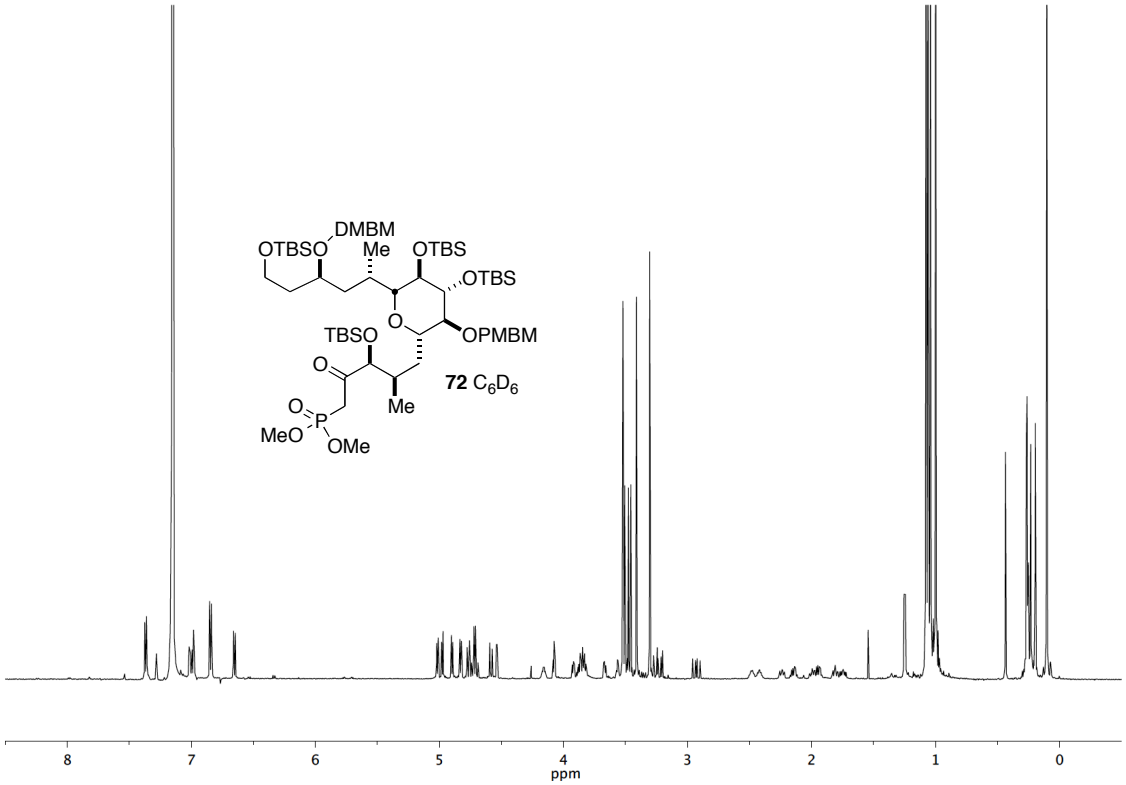


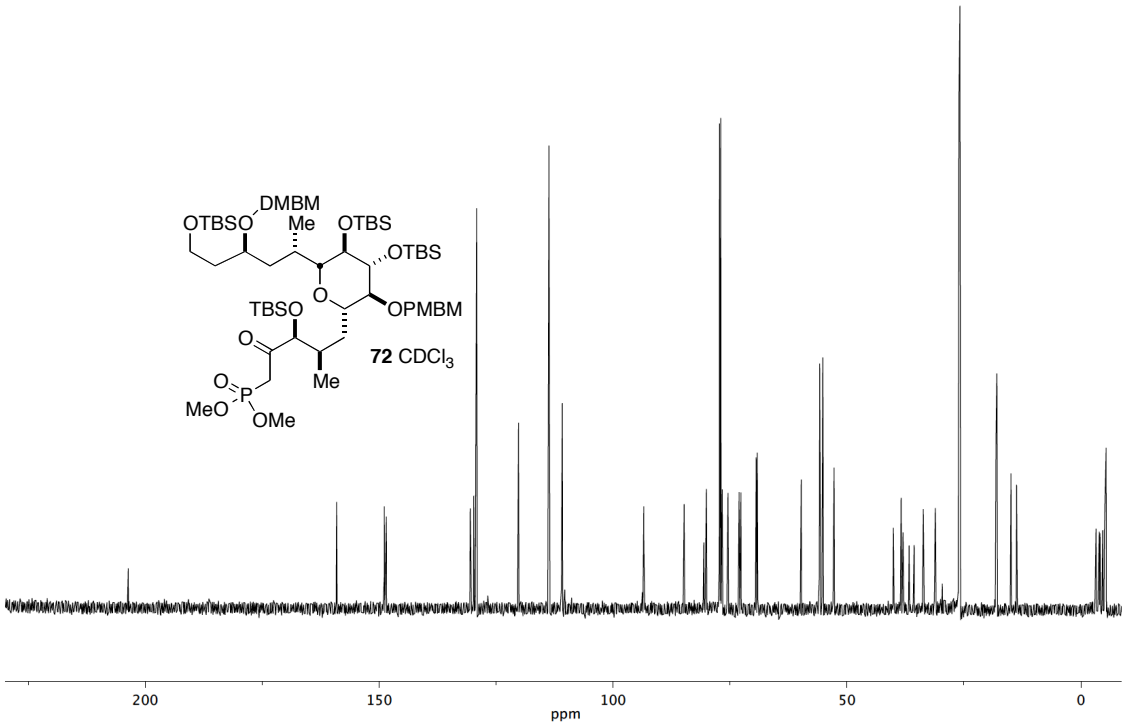

**70** $CDCl_3$


DMBM
OTBSO
Me
OTBS
OTBS
O
TBSO
OPMBM
Me
70 C6D6
8
7
6
5
4
3
2
1
0
ppm

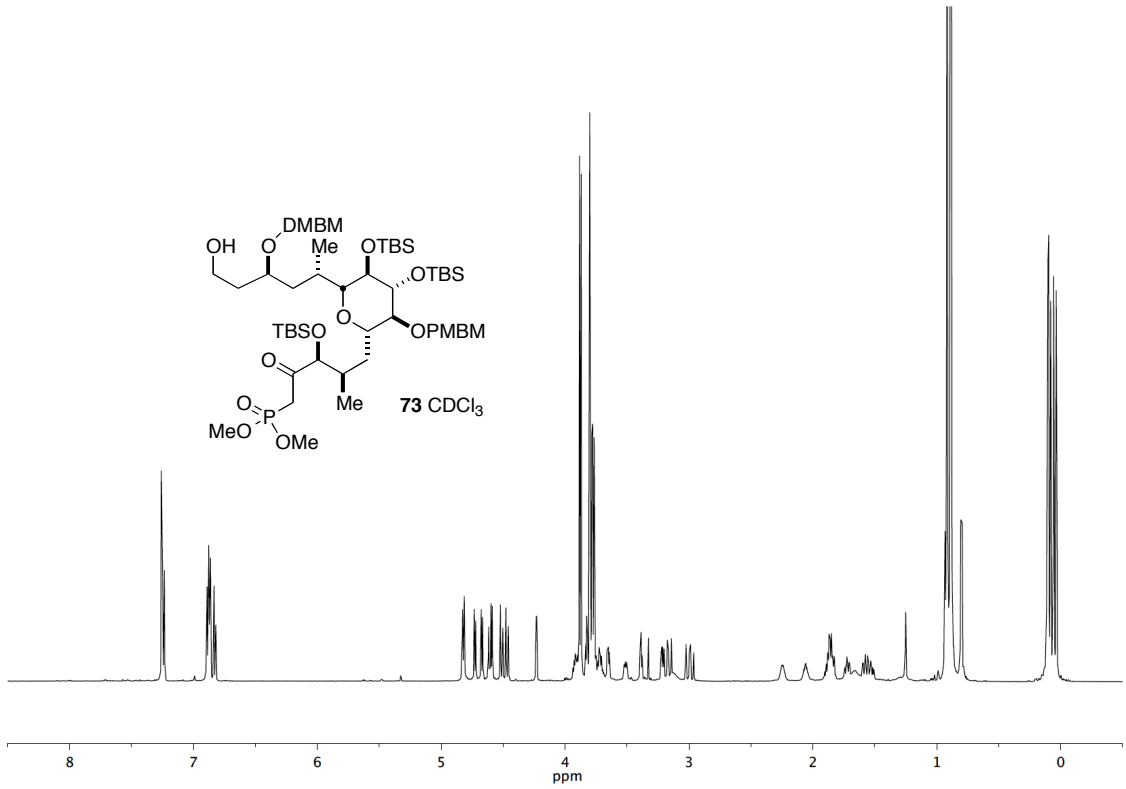

DMBM
OTBSO
Me
OTBS
OTBS
O
TBSO
OPMBM
Me
70 CDCl3
200
150
100
50
0
ppm


DMBM
OTBSO
Me
OTBS
OTBS
O
TBSO
OPMBM
O
Me
O
P
MeO
OMe
72 CDCl3
8
7
6
5
4
ppm
3
2
1
0

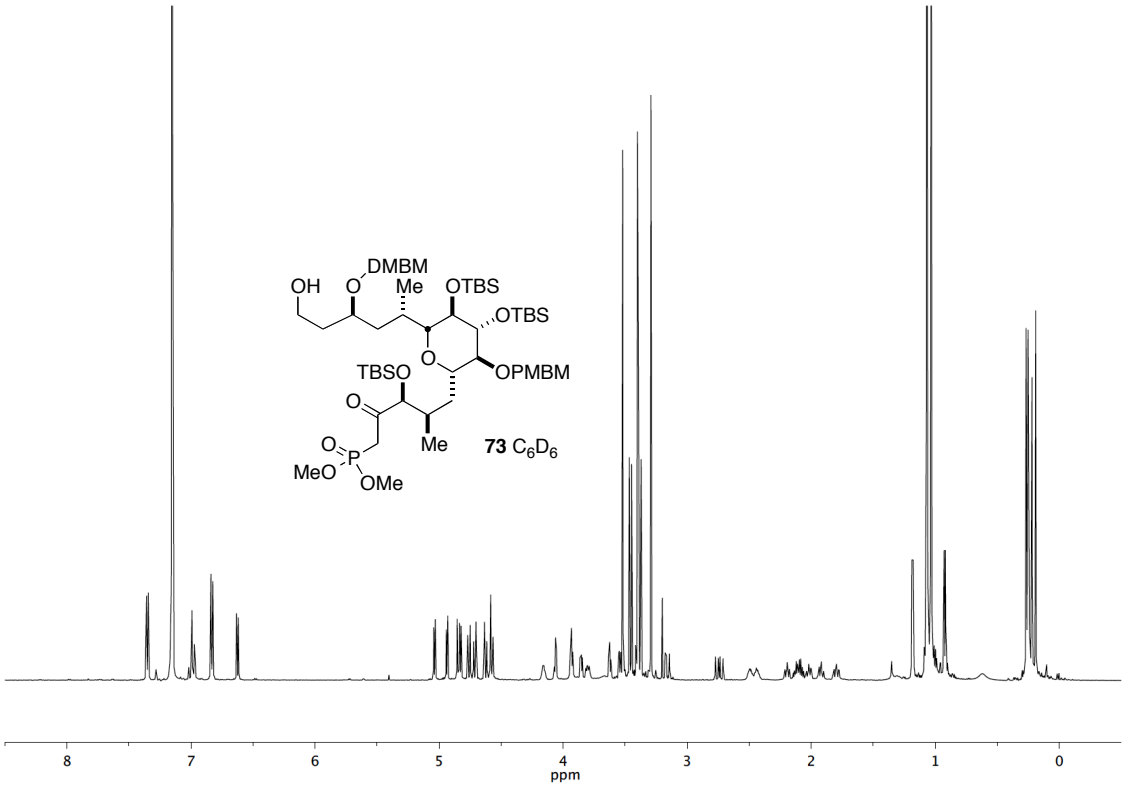

DMBM
OTBSO
Me
OTBS
OTBS
O
TBSO
OPMBM
O
Me
O
P
MeO
OMe
72 C6D6
8
7
6
5
4
ppm
3
2
1
0

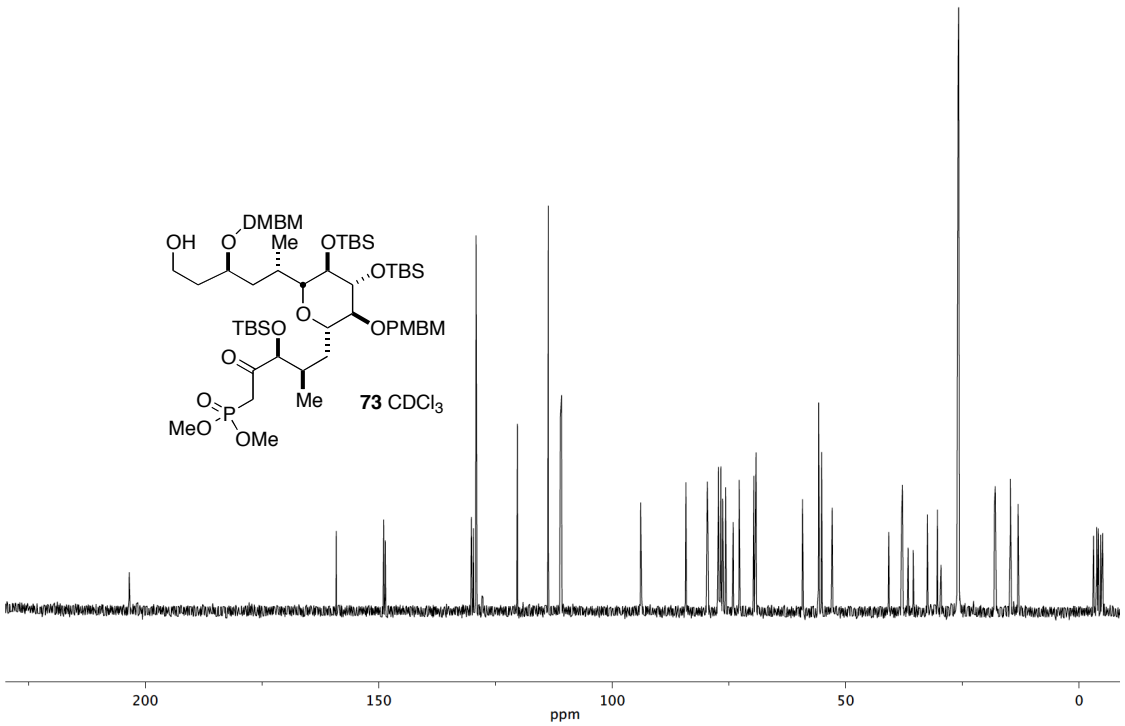


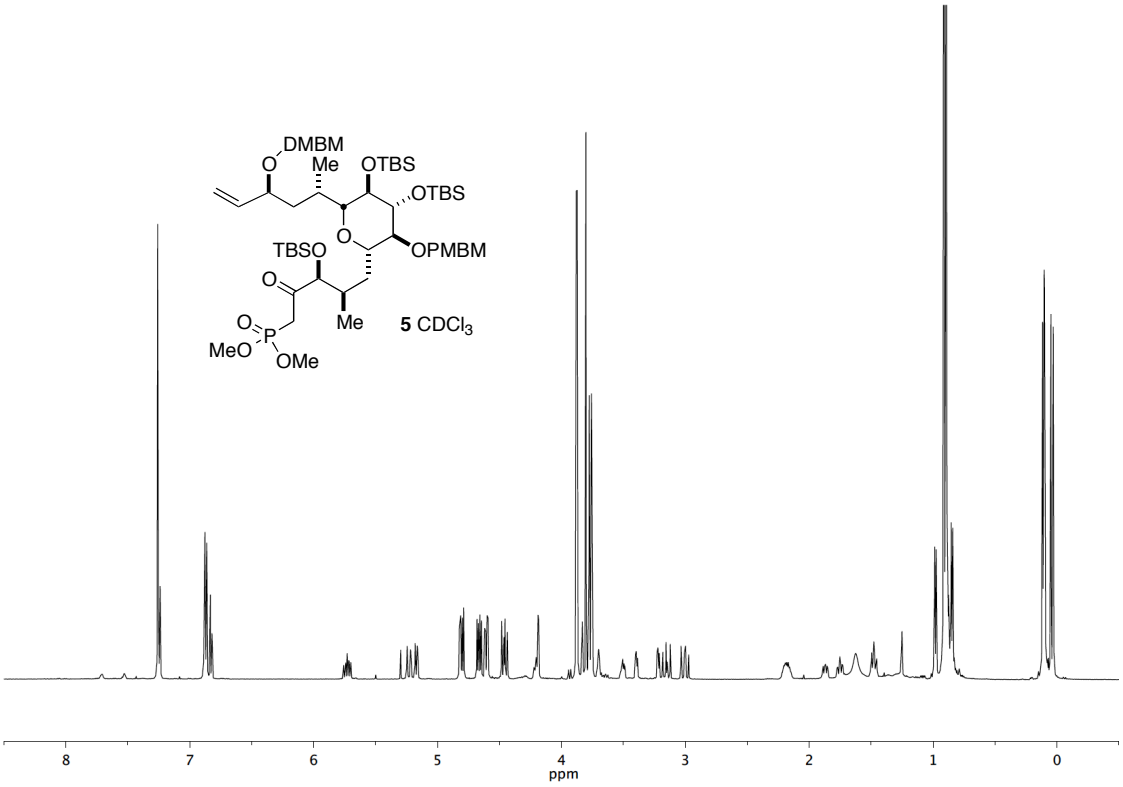

**72** $CDCl_3$

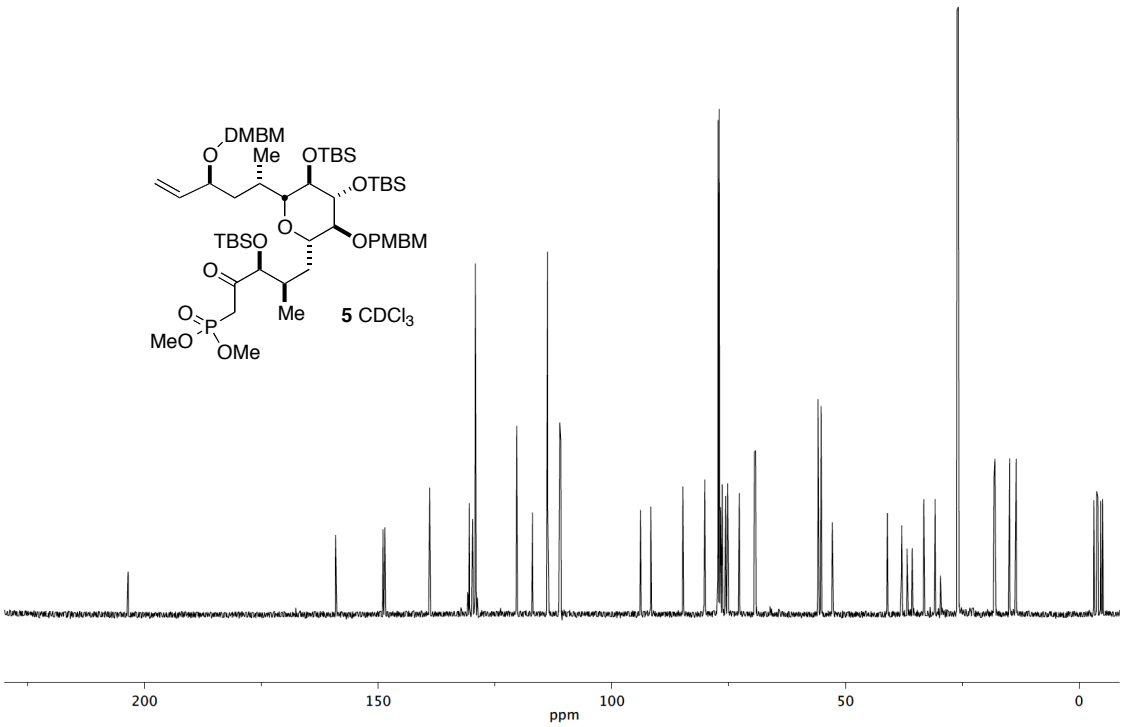


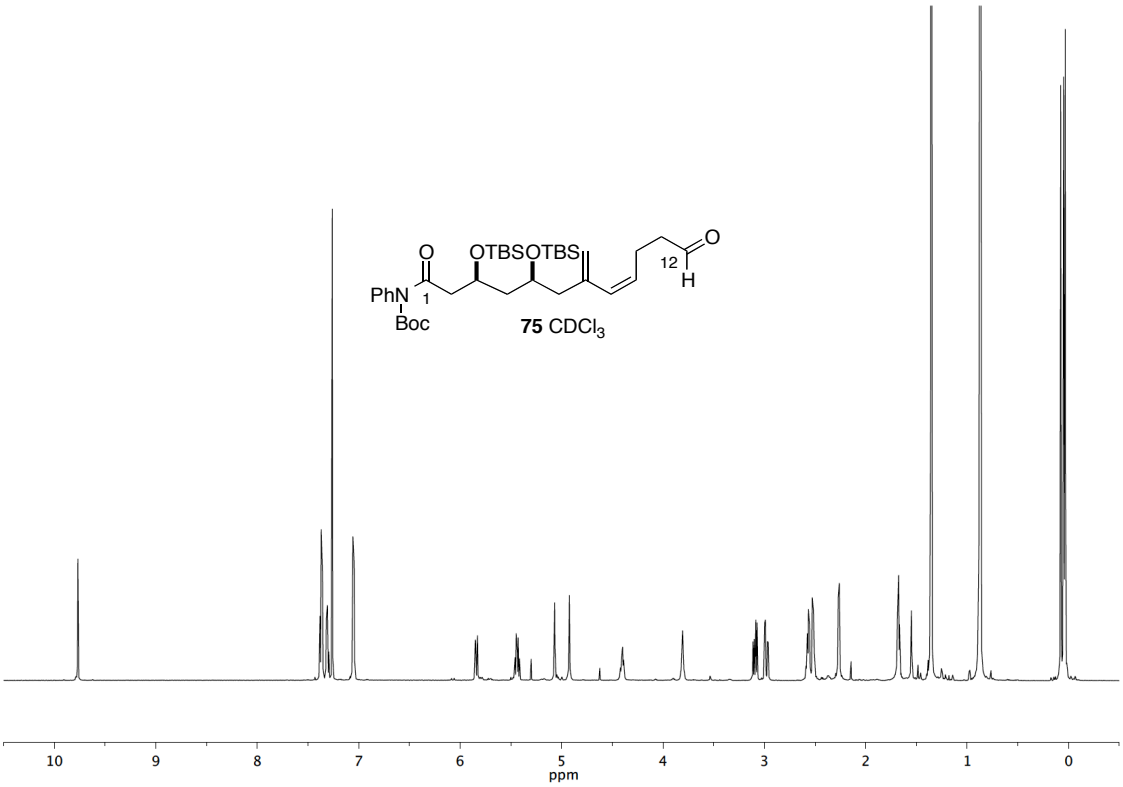

**73** $CDCl_3$

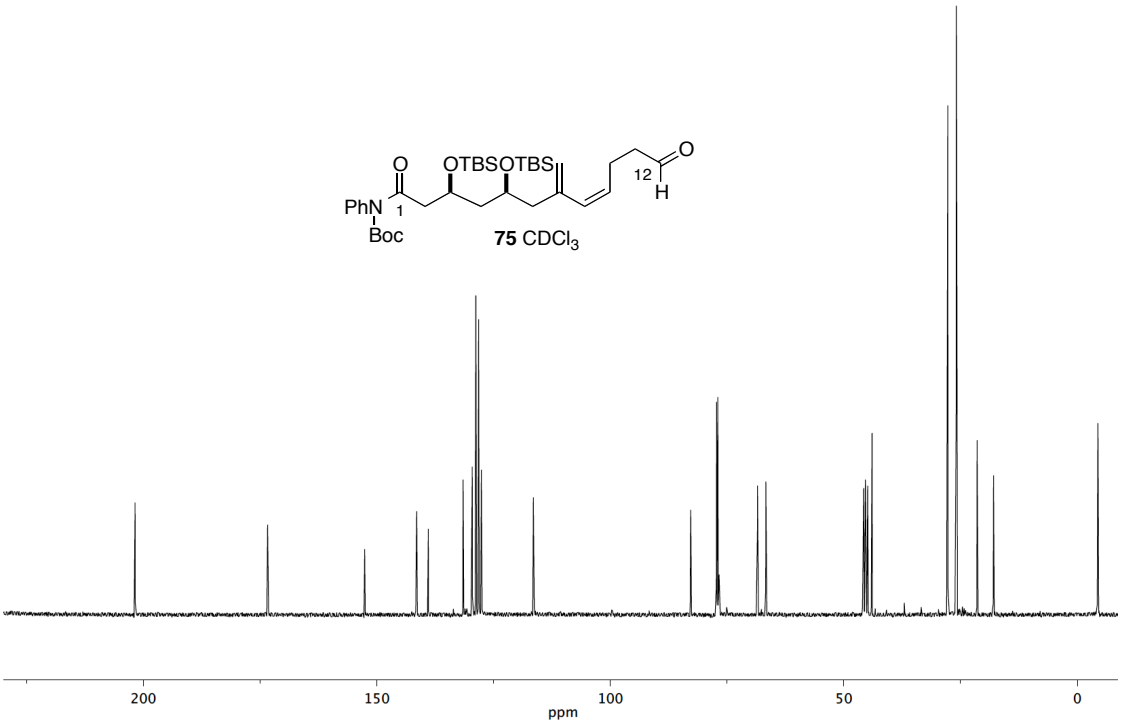

DMBM
OH
O
Me
OTBS
OTBS
O
TBSO
OPMBM
O
Me
O
P
MeO
OMe
73 C6D6
8
7
6
5
4
3
2
1
0
ppm

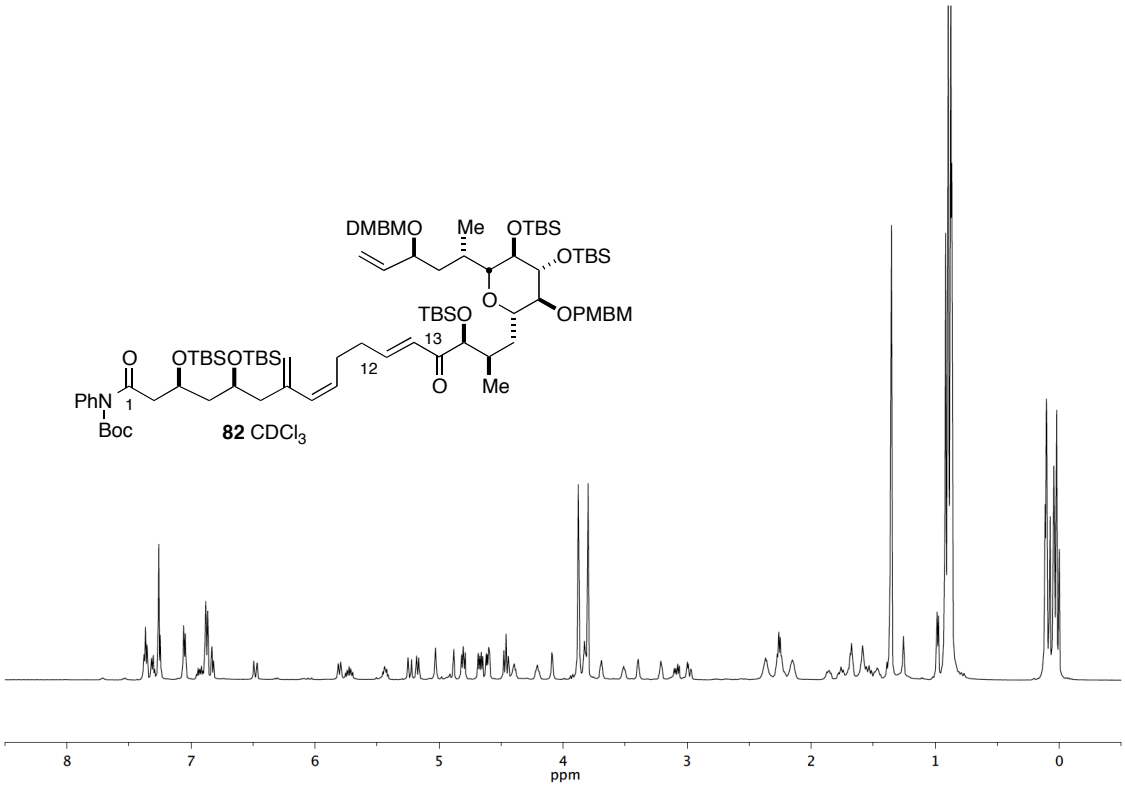

DMBM
OH
O
Me
OTBS
OTBS
O
TBSO
OPMBM
O
Me
O
P
MeO
OMe
73 CDCl3
200
150
100
50
0
ppm

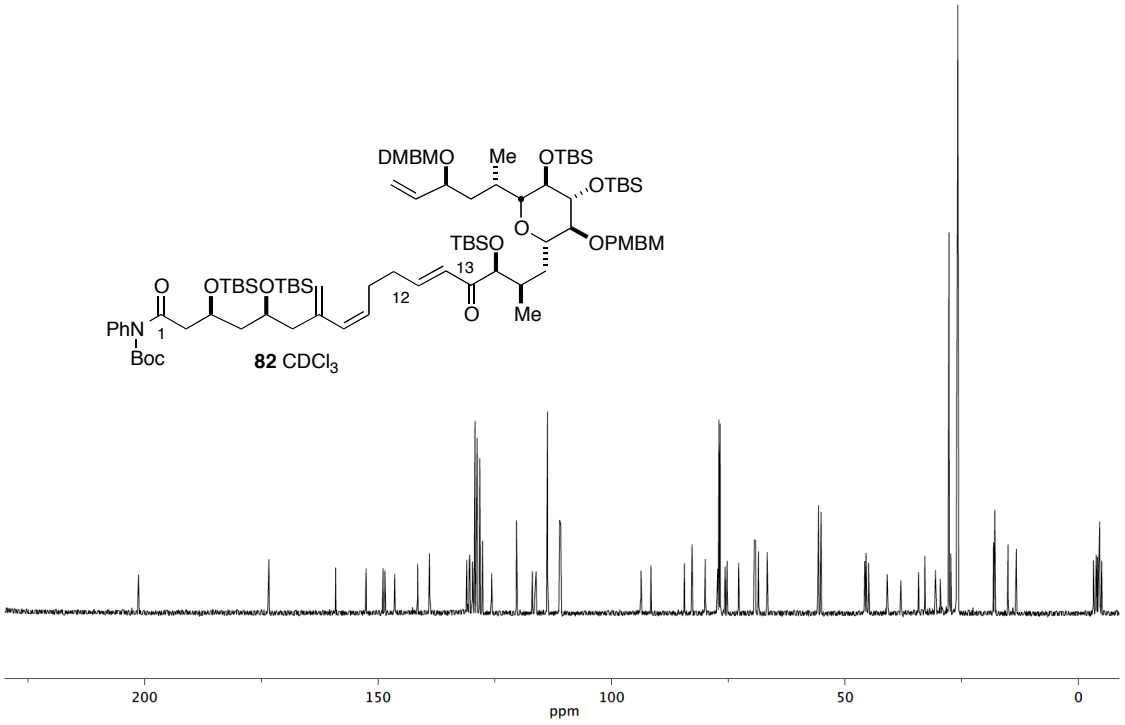

DMBM
O
Me
OTBS
OTBS
O
TBSO
OPMBM
O
Me
O
P
MeO
OMe
5 CDCl3
8
7
6
5
4
3
2
1
0
ppm

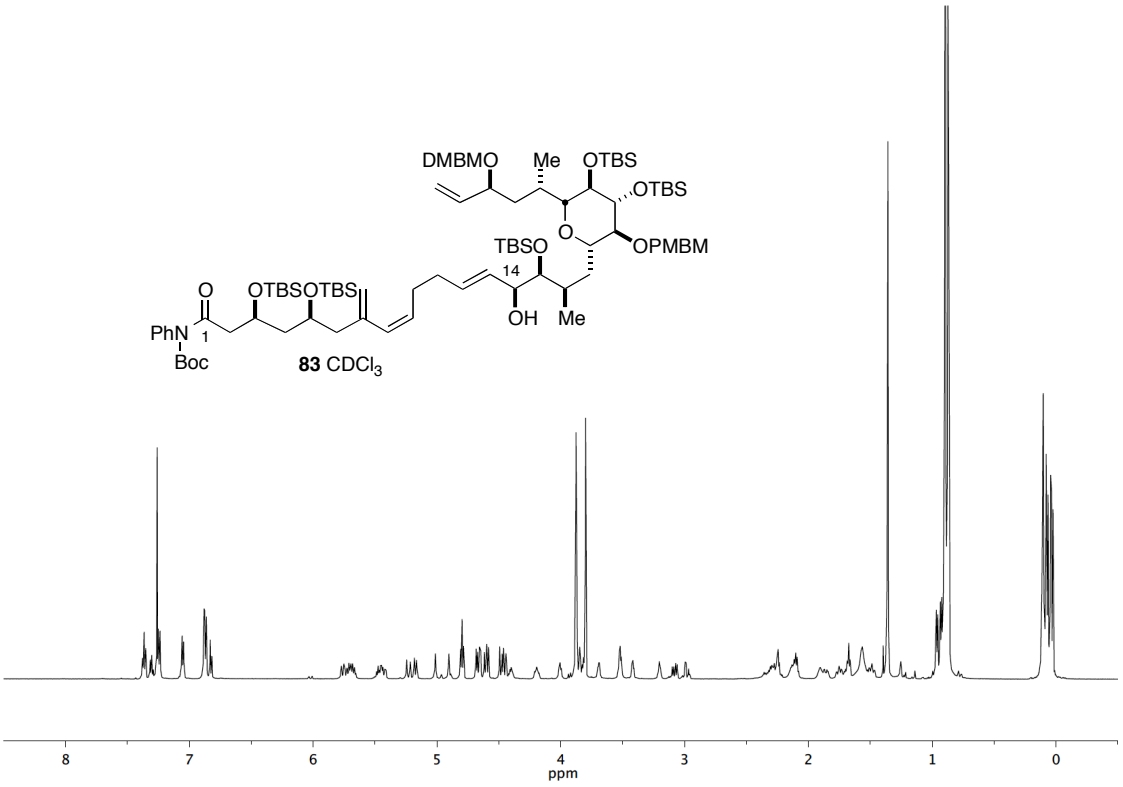

DMBM
O
Me
OTBS
OTBS
O
TBSO
OPMBM
O
Me
O
P
MeO
OMe
5 CDCl3
200
150
100
50
0
ppm

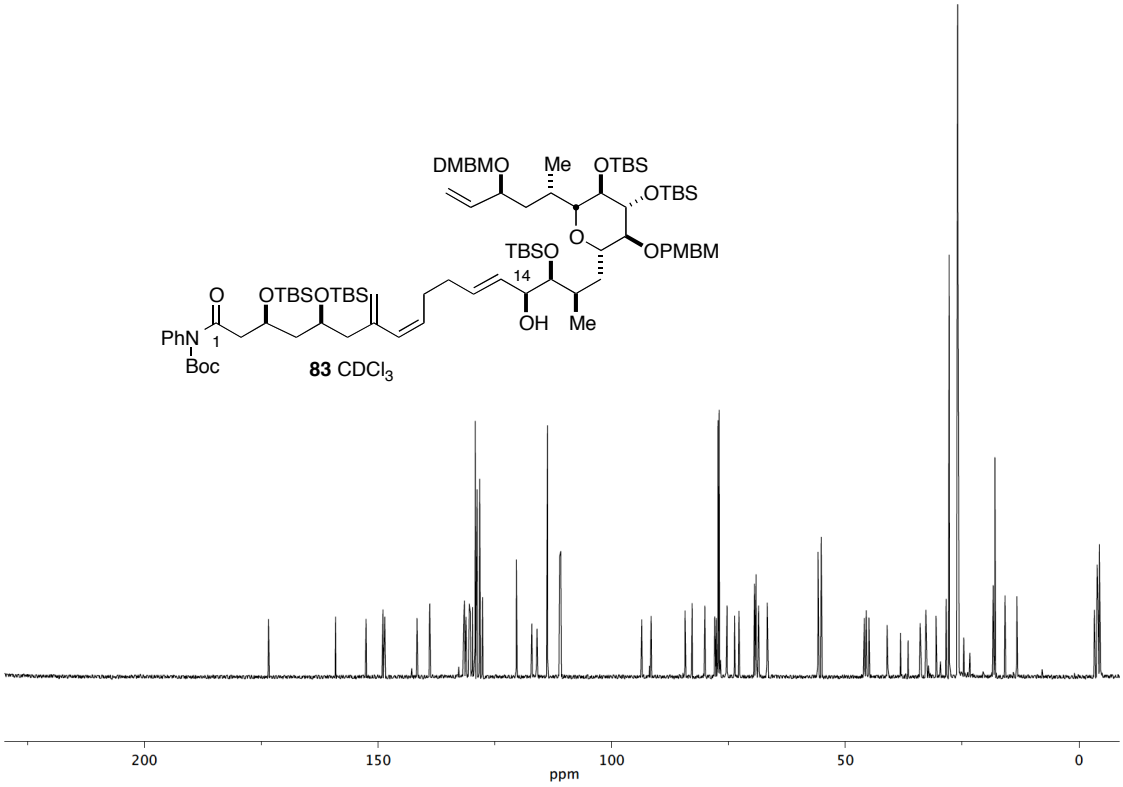

O
OTBSOTBS
12
O
H
PhN
1
Boc
75 CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm

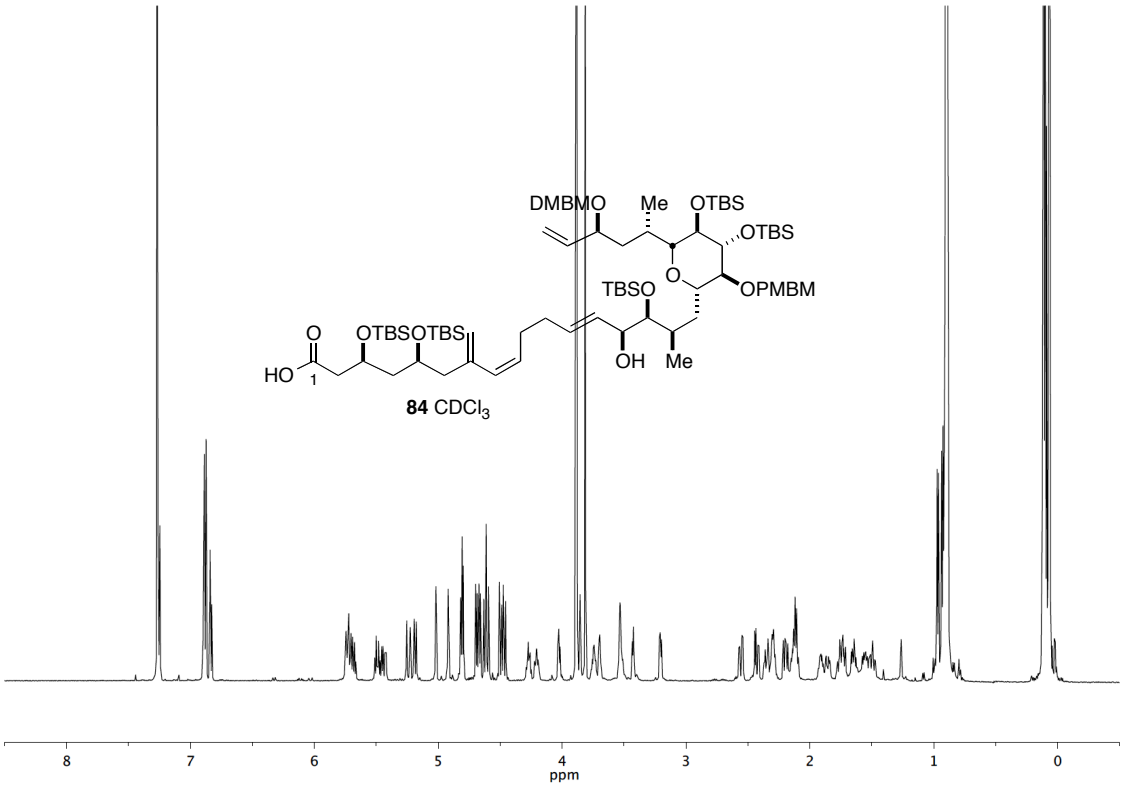

O
OTBSOTBS
12
O
H
PhN
1
Boc
75 CDCl3
200
150
100
50
0
ppm


DMBMO
Me
OTBS
OTBS
O
TBSO
OPMBM
13
12
O
OTBSOTBS
O
Me
PhN
1
Boc
82 CDCl3
8
7
6
5
4
3
2
1
0
ppm

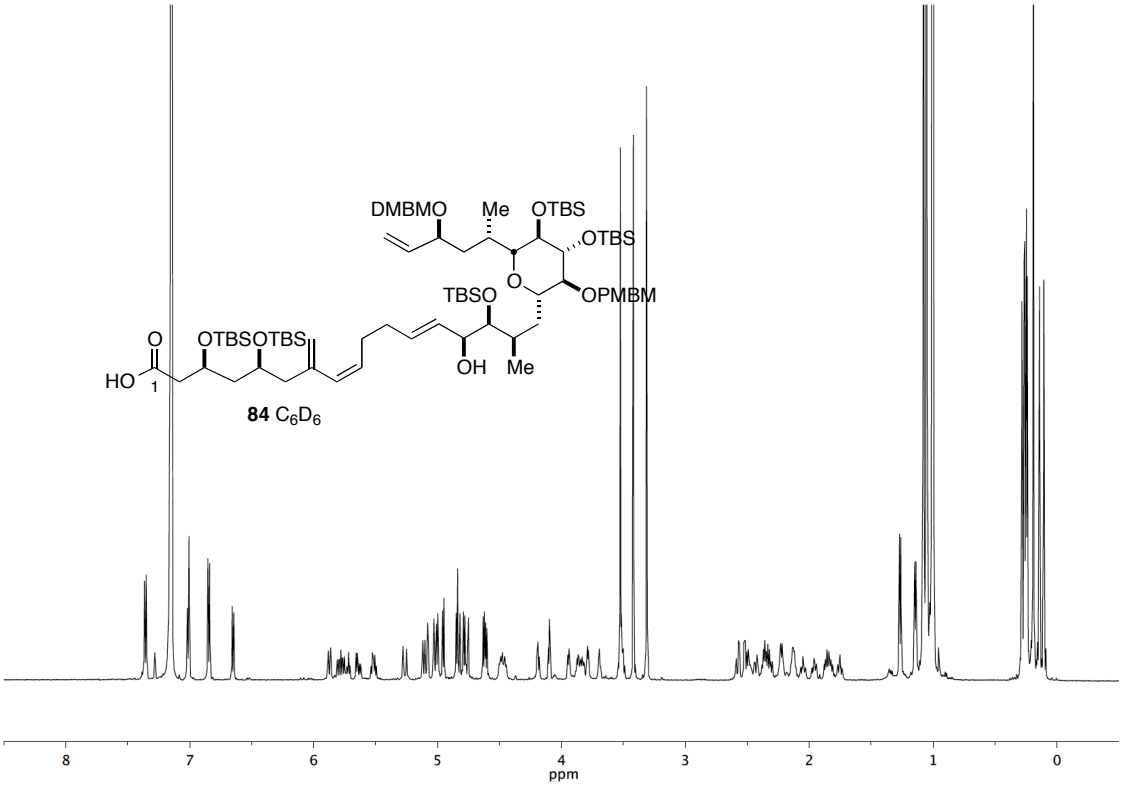

DMBMO
Me
OTBS
OTBS
O
TBSO
OPMBM
13
12
O
OTBSOTBS
O
Me
PhN
1
Boc
82 CDCl3
200
150
100
50
0
ppm


DMBMO
Me
OTBS
OTBS
O
TBSO
OPMBM
14
O
OTBSOTBS
OH
Me
PhN
1
Boc
83 CDCl3
8
7
6
5
4
3
2
1
0
ppm

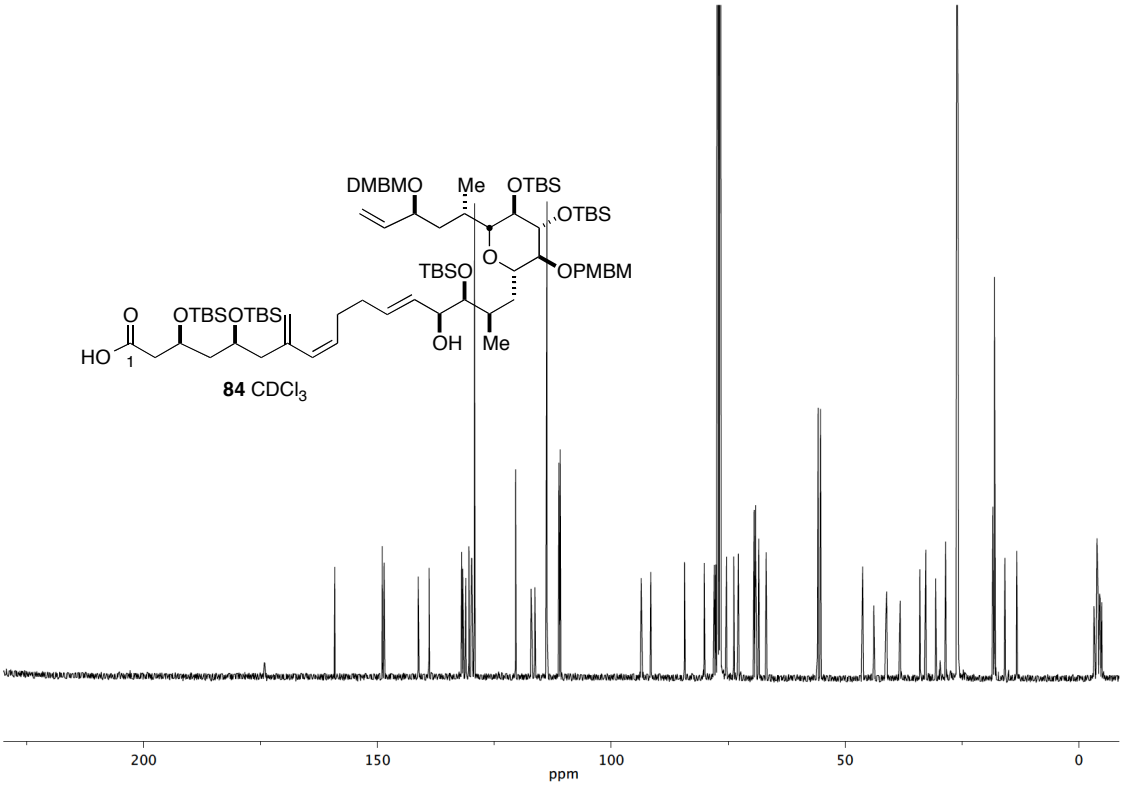

DMBMO
Me
OTBS
OTBS
O
TBSO
OPMBM
14
O
OTBSOTBS
OH
Me
PhN
1
Boc
83 CDCl3
200
150
100
50
0
ppm

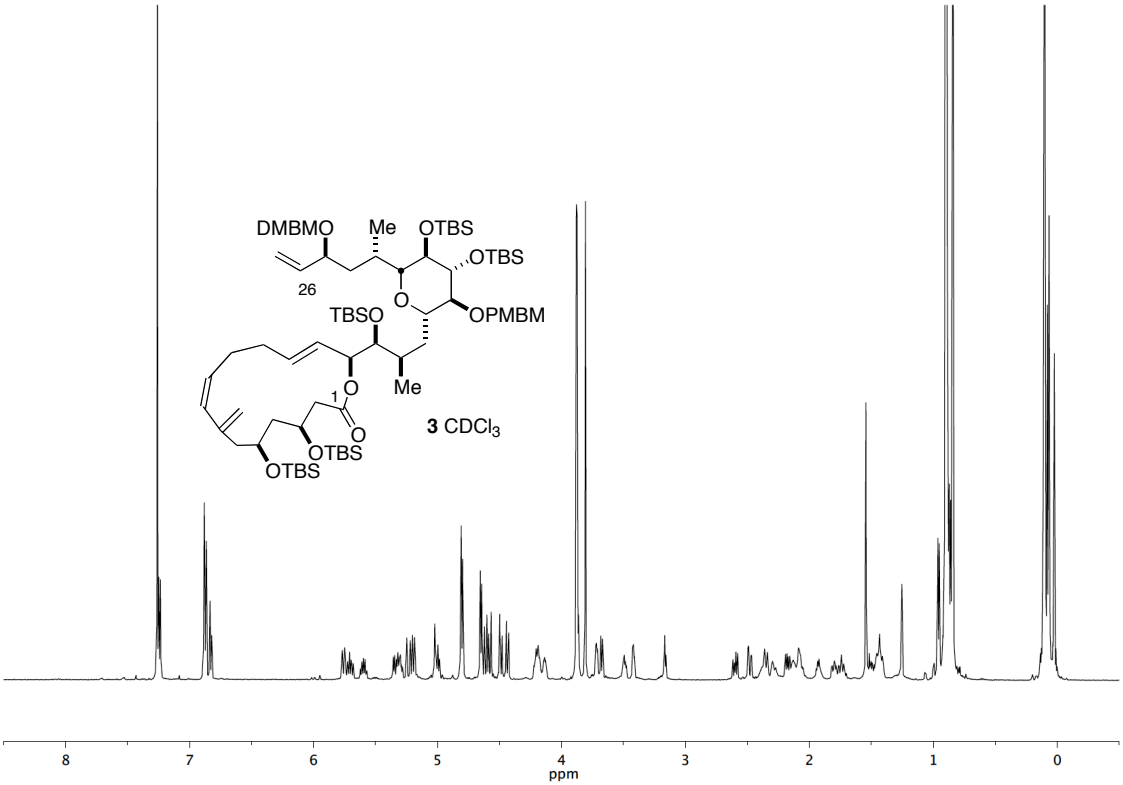


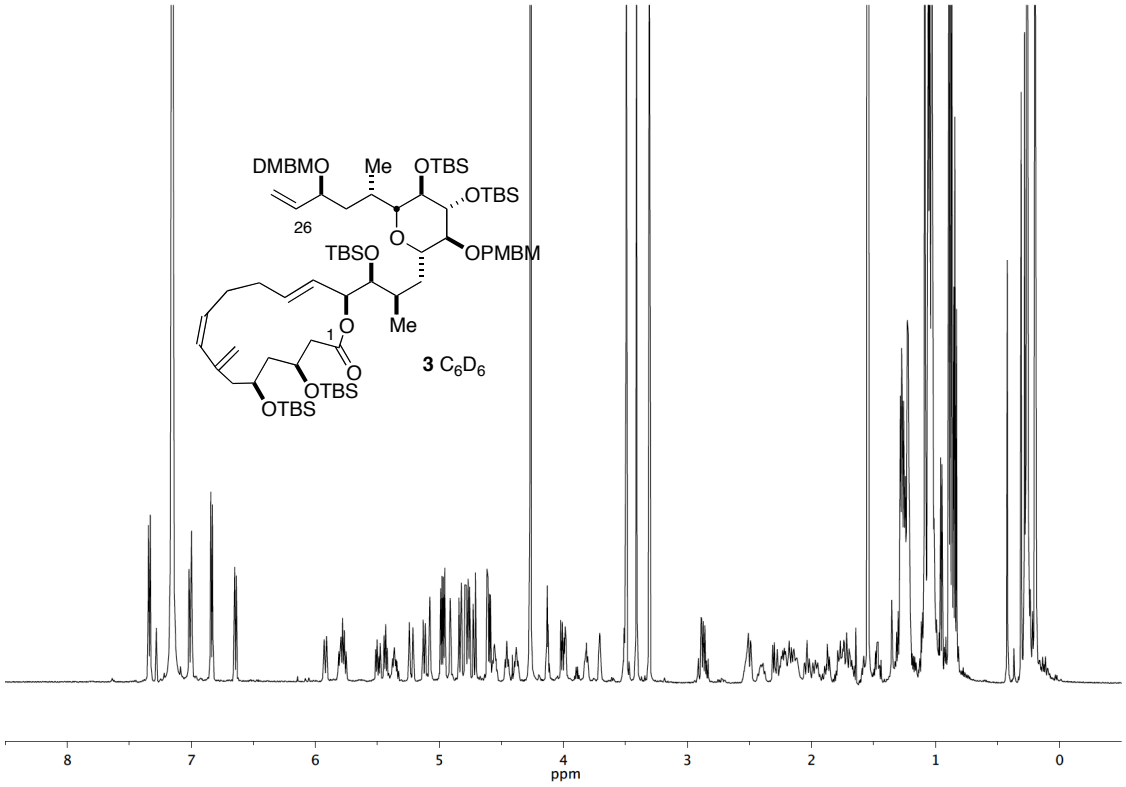

**84** $CDCl_3$

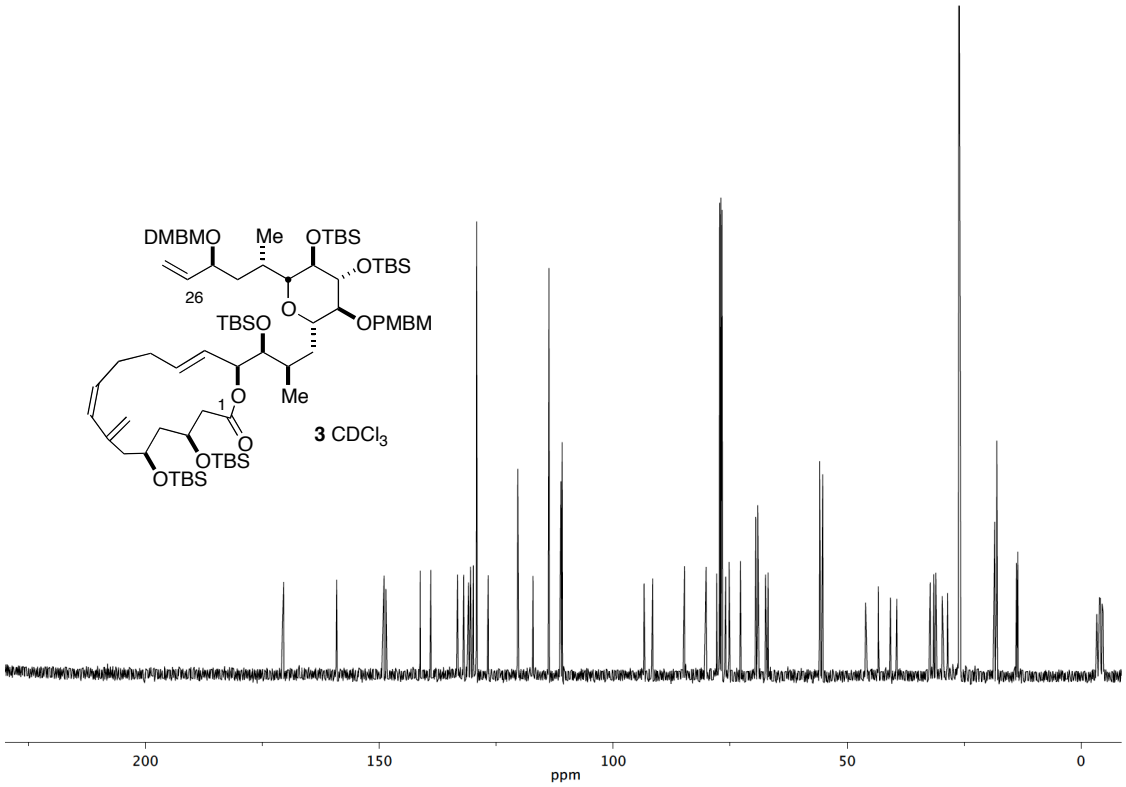



**84** $C_6D_6$

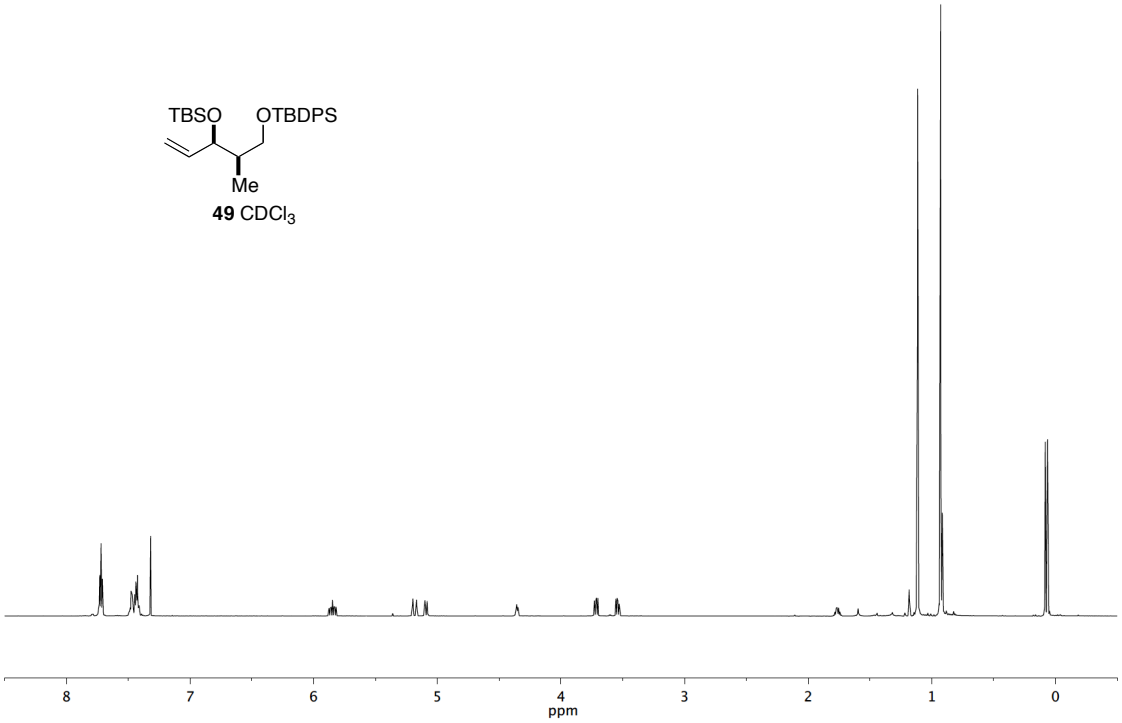

DMBMO
Me
OTBS
OTBS
TBSO
OPMBM
O
OTBSOTBS
HO
1
OH
Me
84 CDCl3
200
150
100
50
0
ppm

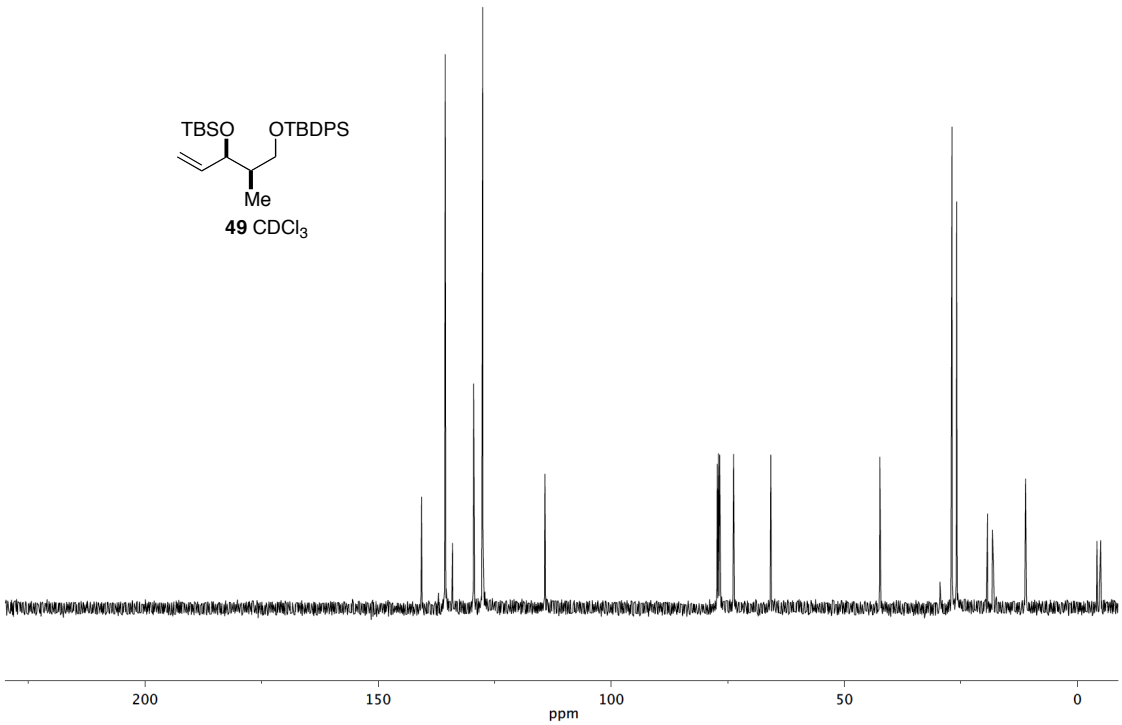

DMBMO
Me
OTBS
OTBS
26
O
TBSO
OPMBM
Me
1
O
O
OTBS
OTBS
3 CDCl3
8
7
6
5
4
3
2
1
0
ppm

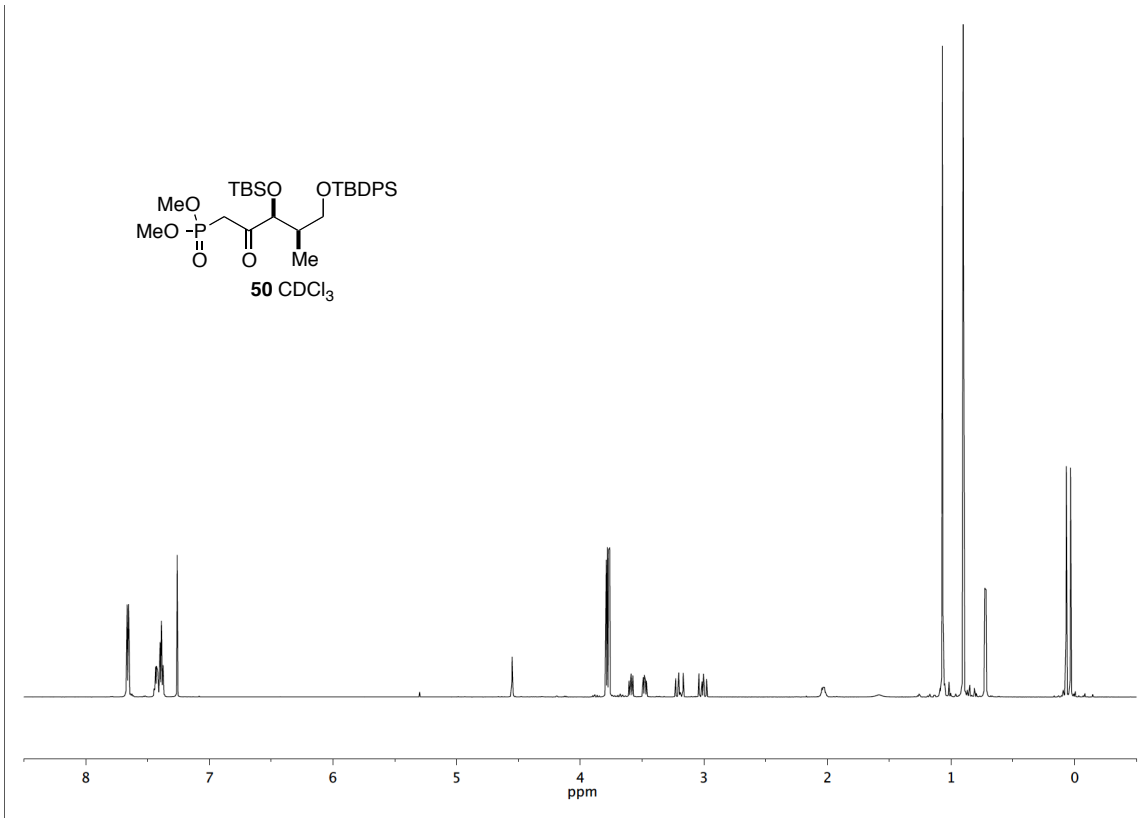

DMBMO
Me
OTBS
OTBS
26
O
TBSO
OPMBM
Me
1
O
O
OTBS
OTBS
3 C6D6
8
7
6
5
4
3
2
1
0
ppm

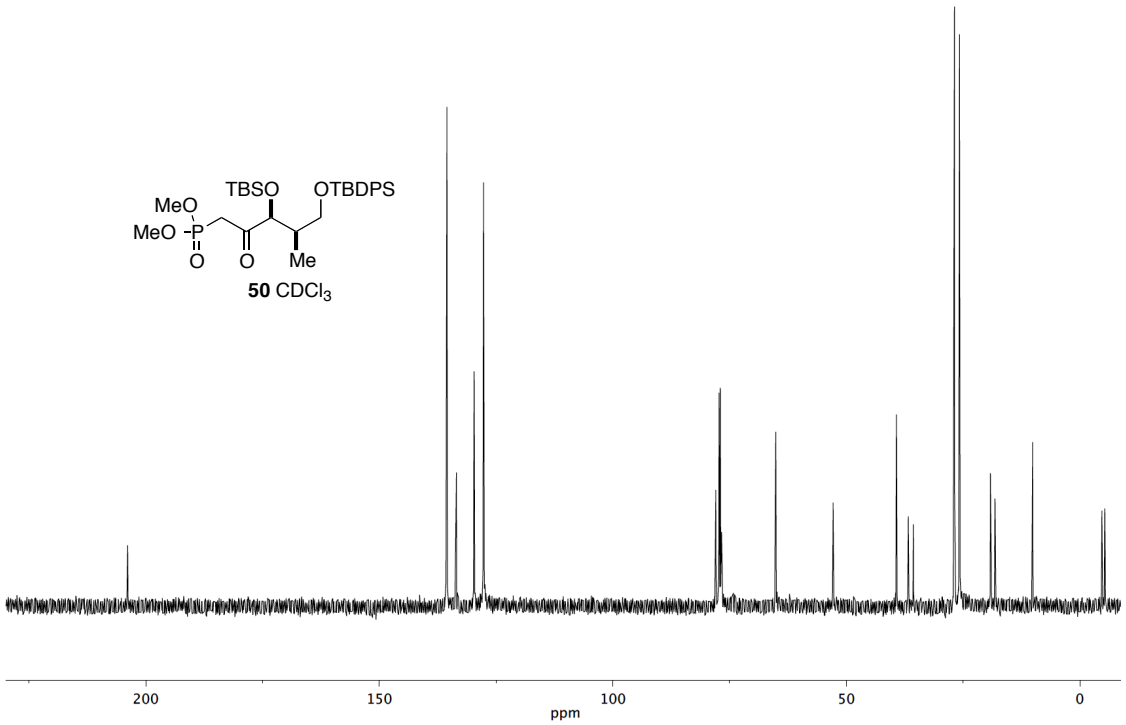

DMBMO
Me
OTBS
OTBS
26
O
TBSO
OPMBM
Me
1
O
O
OTBS
OTBS
3 CDCl3
200
150
100
50
0
ppm

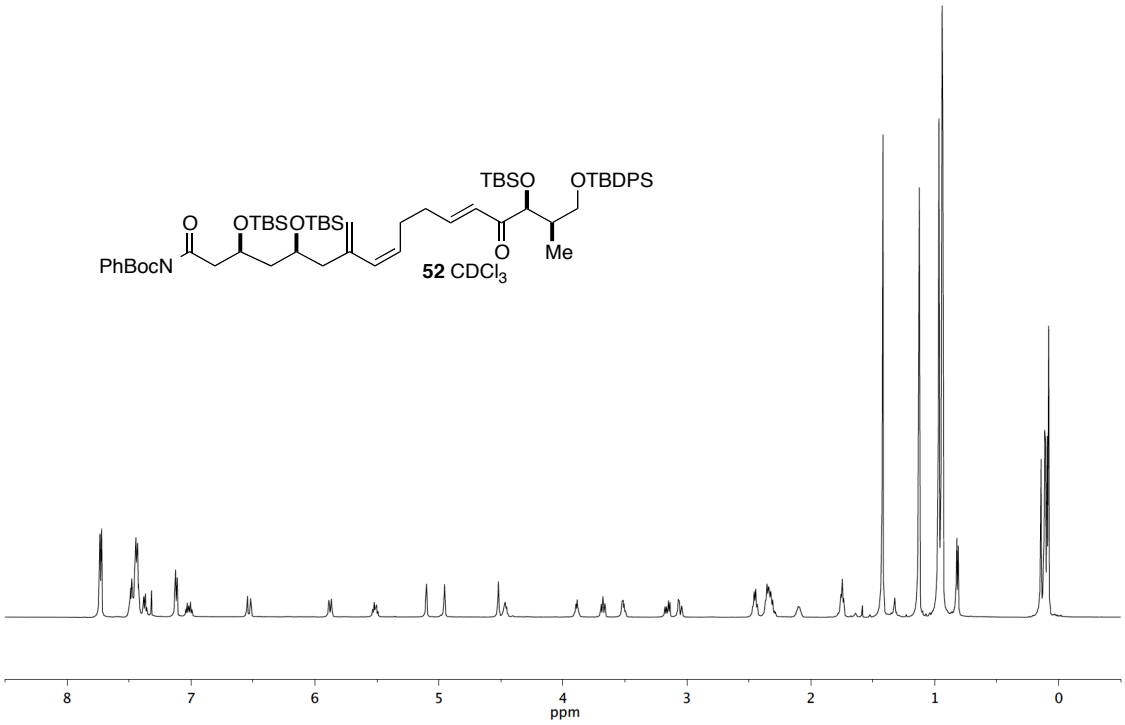
# III. NMR Spectra From Chapter 5

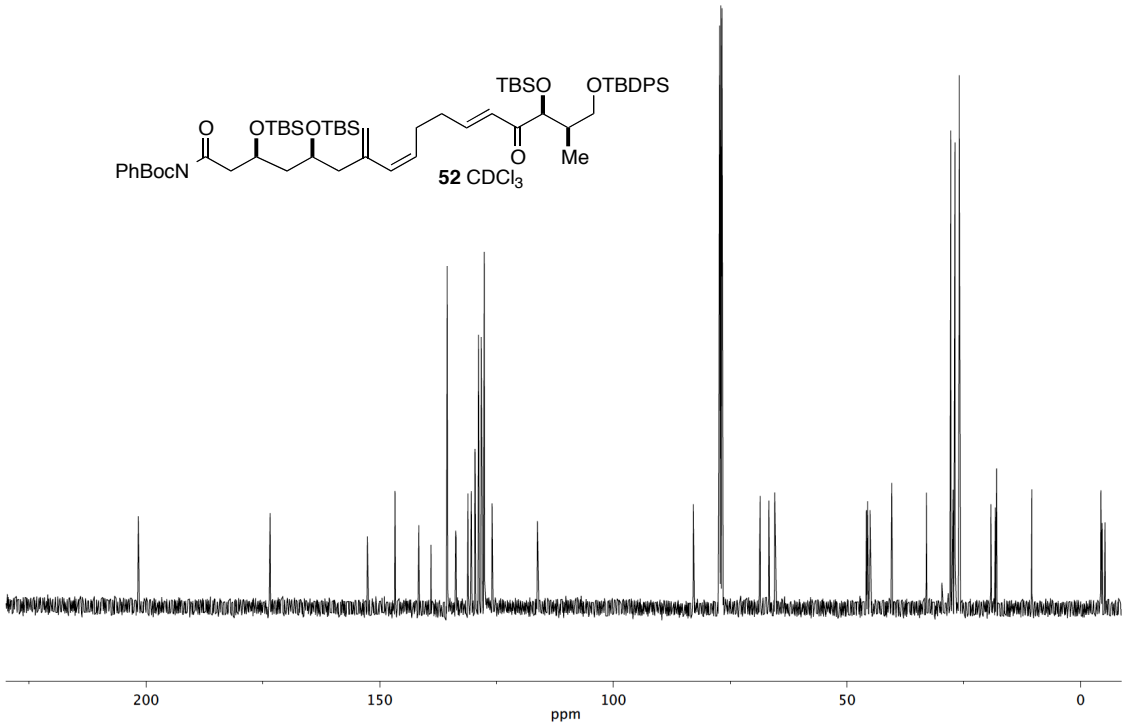


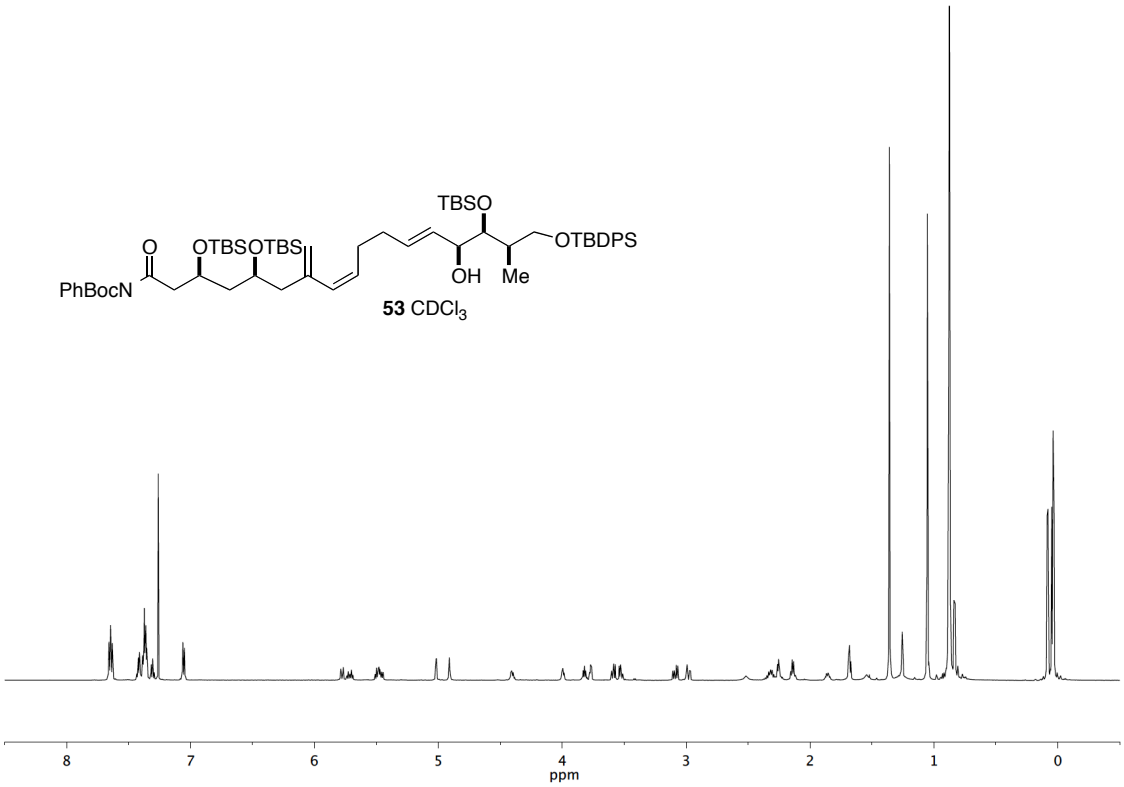



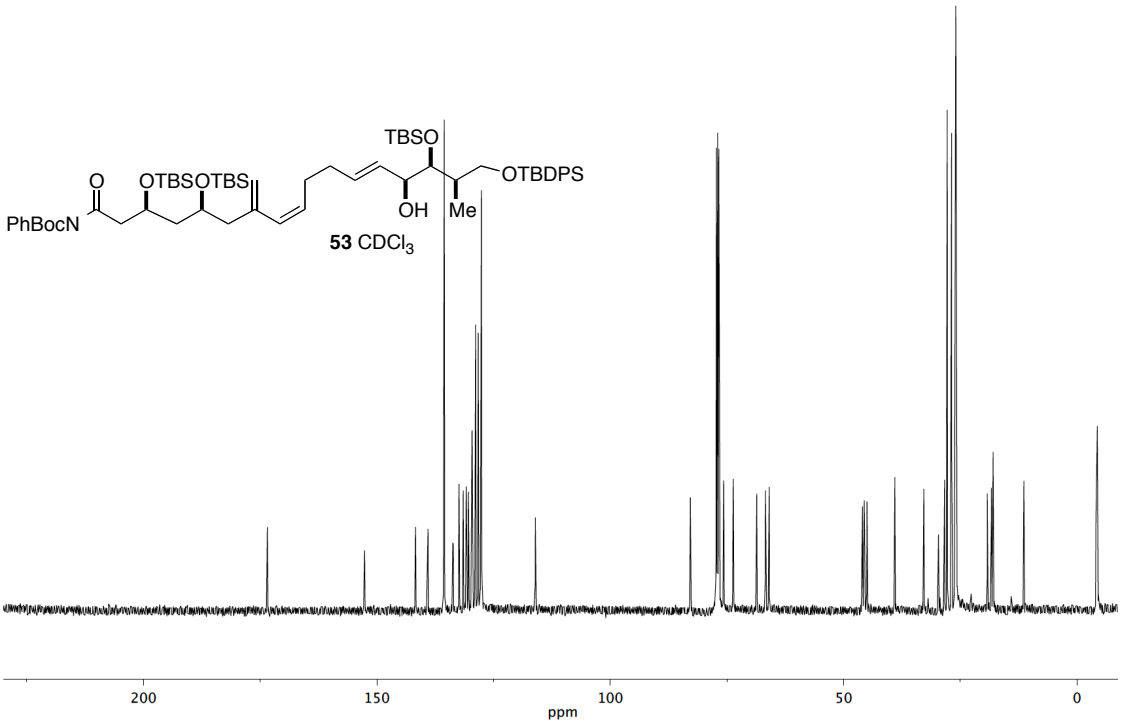

TBSO
OTBDPS
MeO
MeO
P
O
O
Me
50 CDCl3
8
7
6
5
4
3
2
1
0
ppm

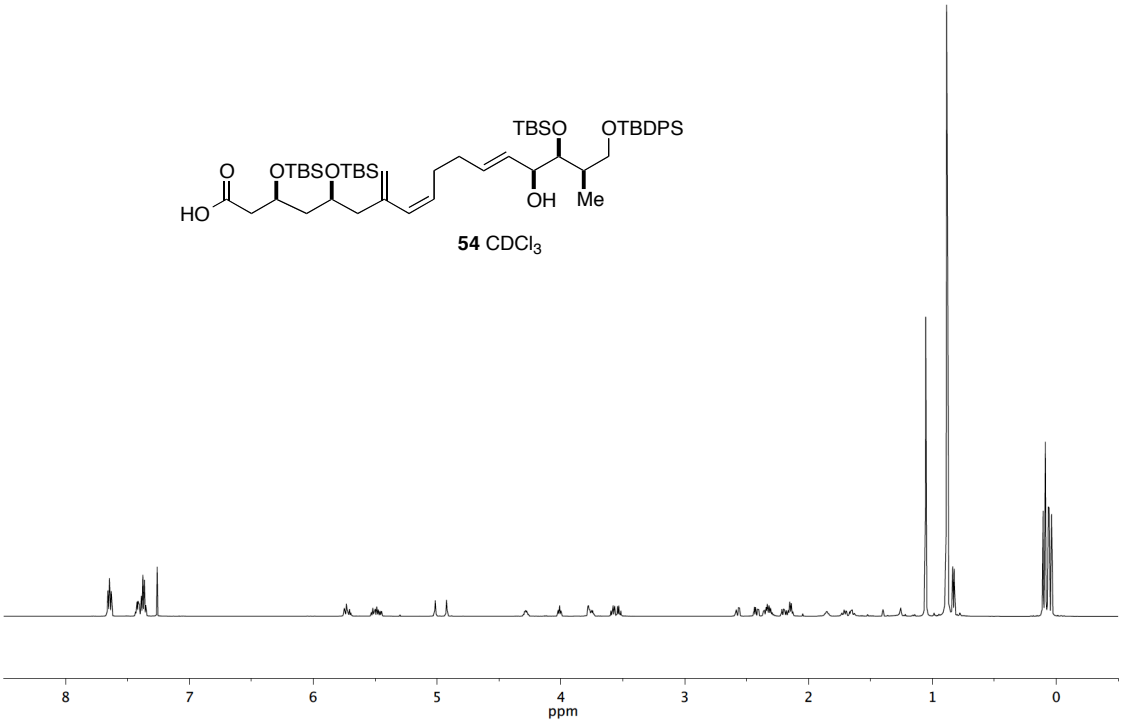

TBSO
OTBDPS
MeO
MeO
P
O
O
Me
50 CDCl3
200
150
100
50
0
ppm


TBSO
OTBDPS
O
OTBSOTBS
PhBocN
O
Me
52 CDCl3
8
7
6
5
4
3
2
1
0
ppm

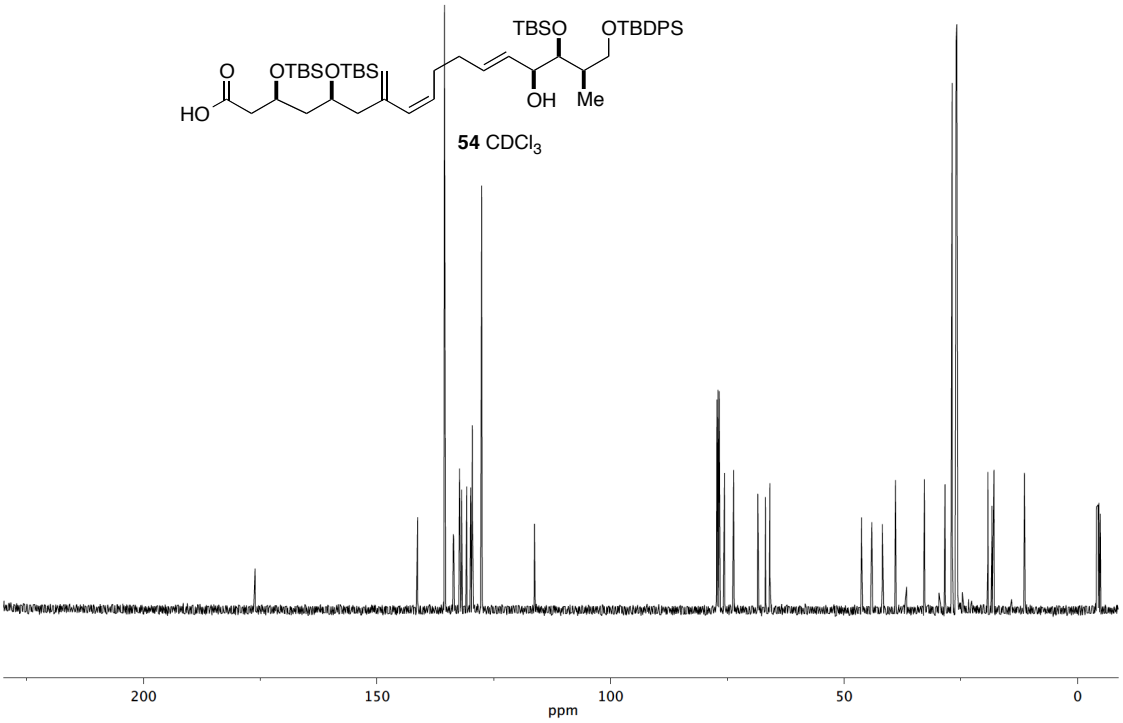

TBSO
OTBDPS
O
OTBSOTBS
PhBocN
O
Me
52 CDCl3
200
150
100
50
0
ppm


TBSO
O
OTBSOTBS
OTBDPS
PhBocN
OH
Me
53 CDCl3
8
7
6
5
4
3
2
1
0
ppm

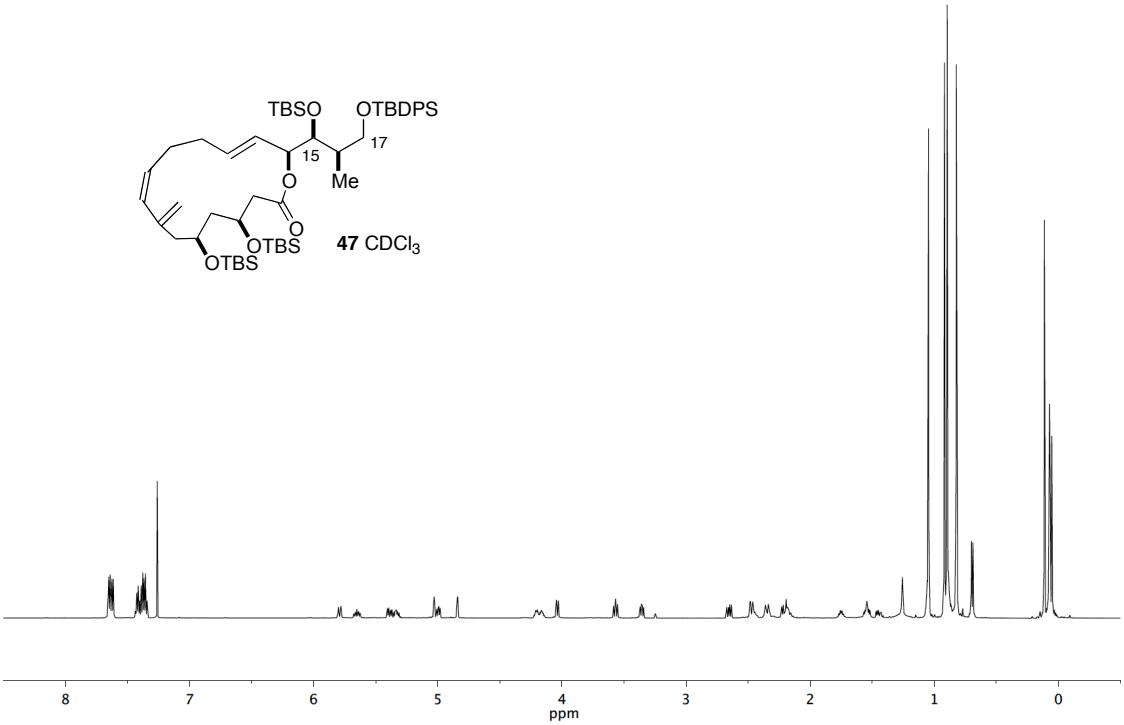

TBSO
O
OTBSOTBS
OTBDPS
PhBocN
OH
Me
53 CDCl3
200
150
100
50
0
ppm

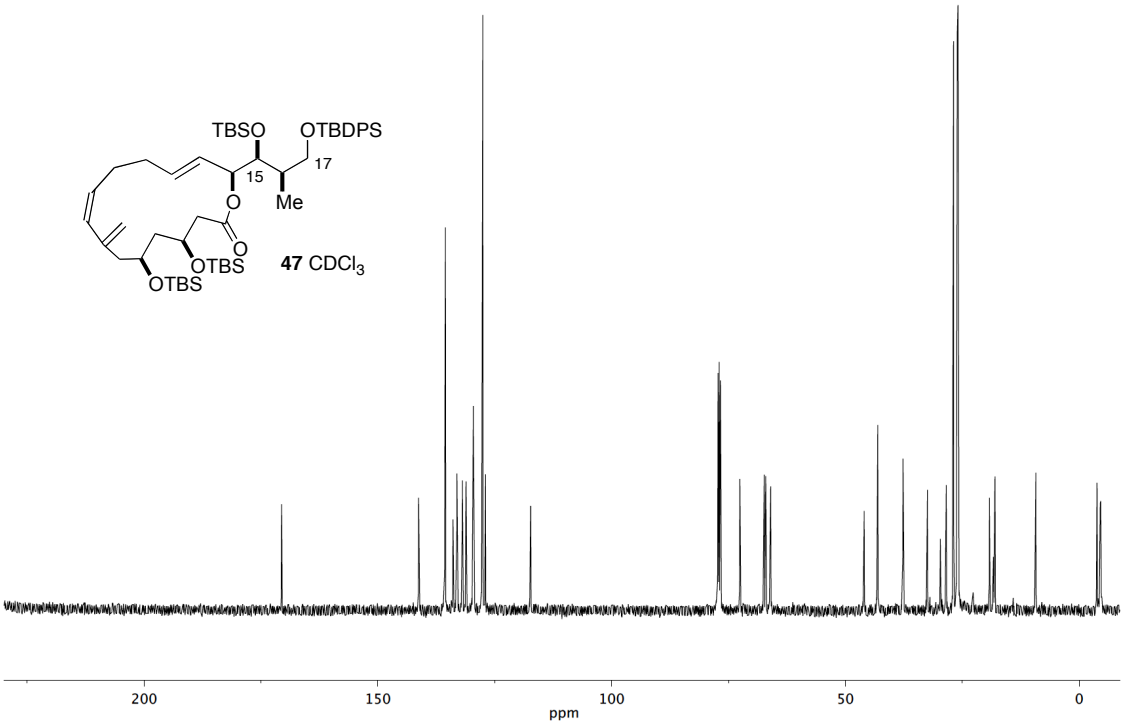


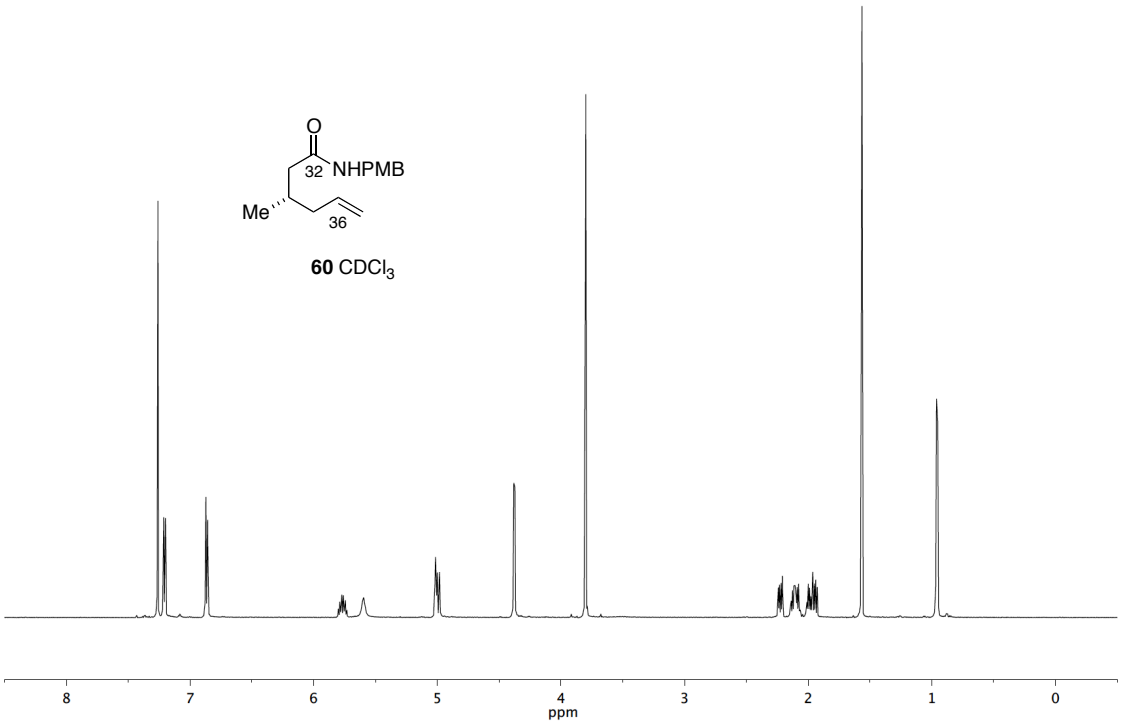

**54** $CDCl_3$



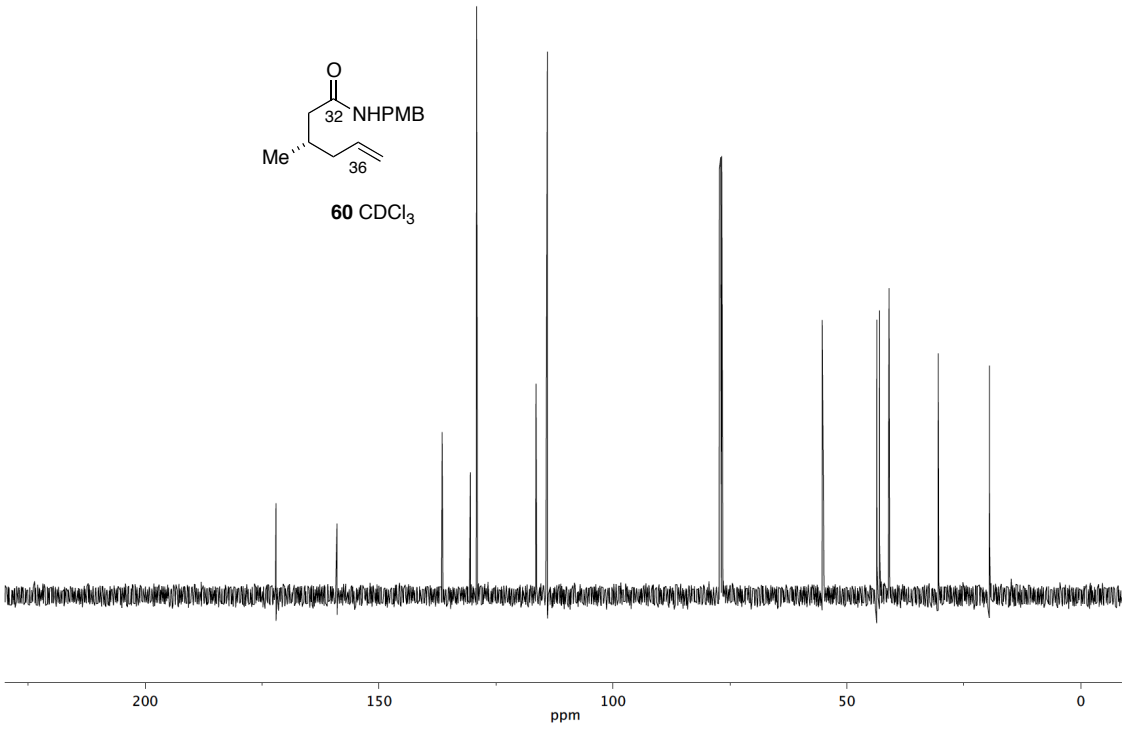

**54** $CDCl_3$


TBSO
OTBDPS
17
15
Me
O
O
OTBS
OTBS
47 CDCl3
8
7
6
5
4
3
2
1
0
ppm

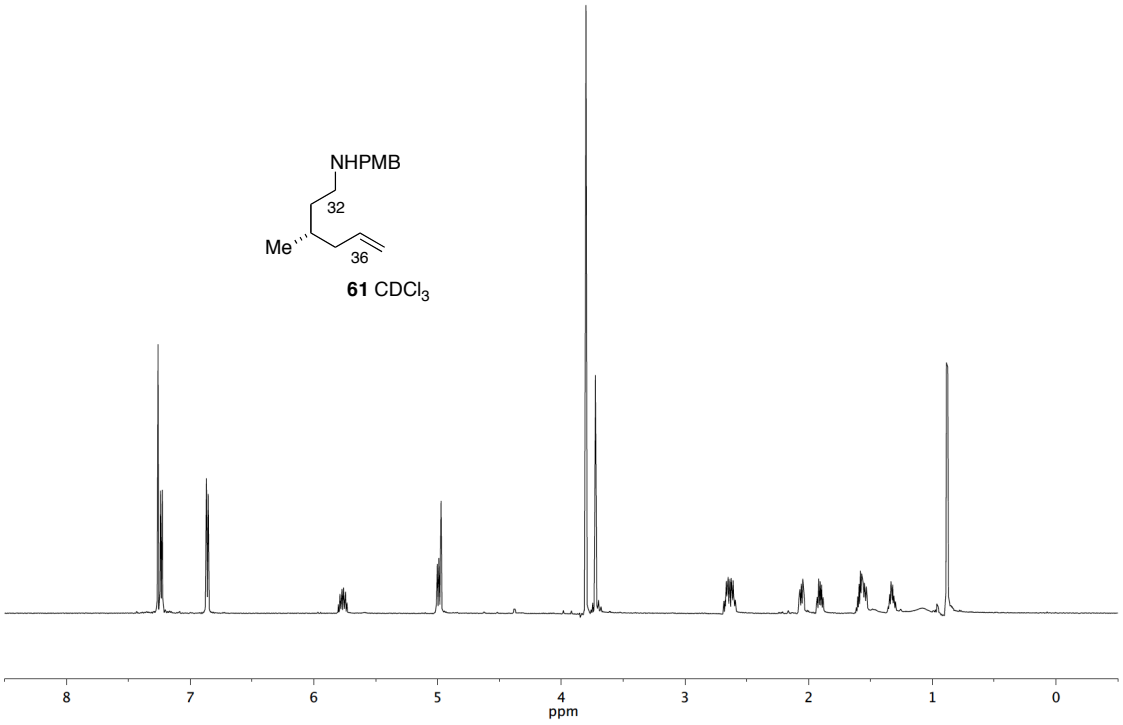

TBSO
OTBDPS
17
15
Me
O
O
OTBS
OTBS
47 CDCl3
200
150
100
50
0
ppm

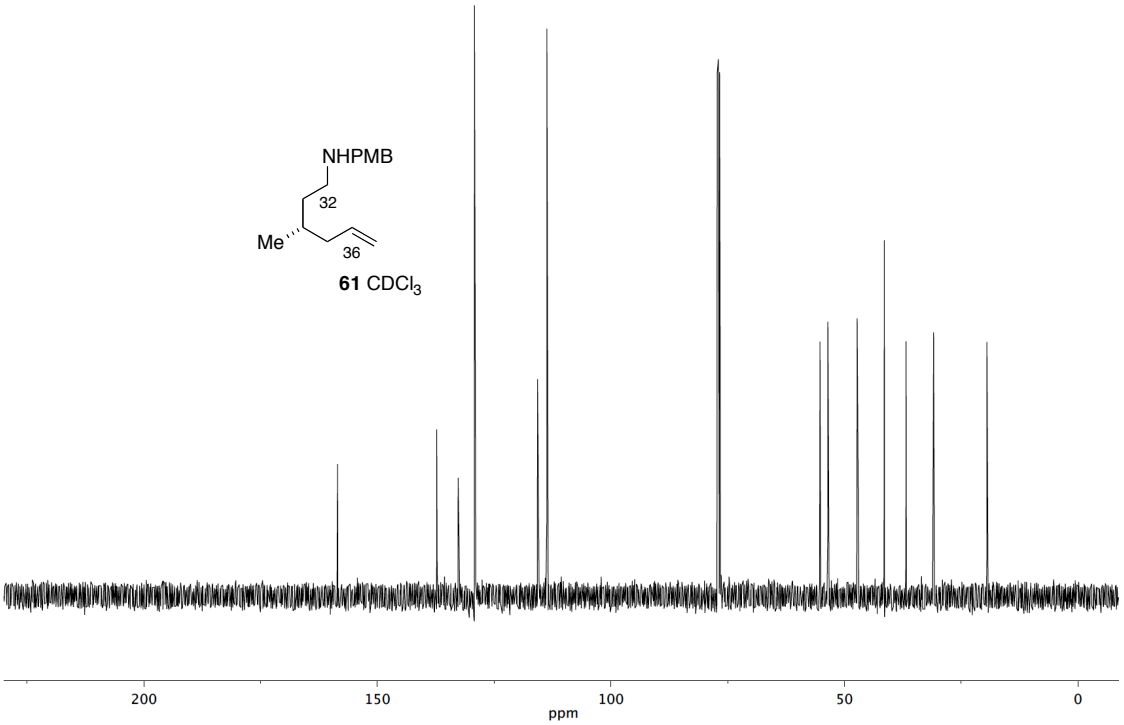


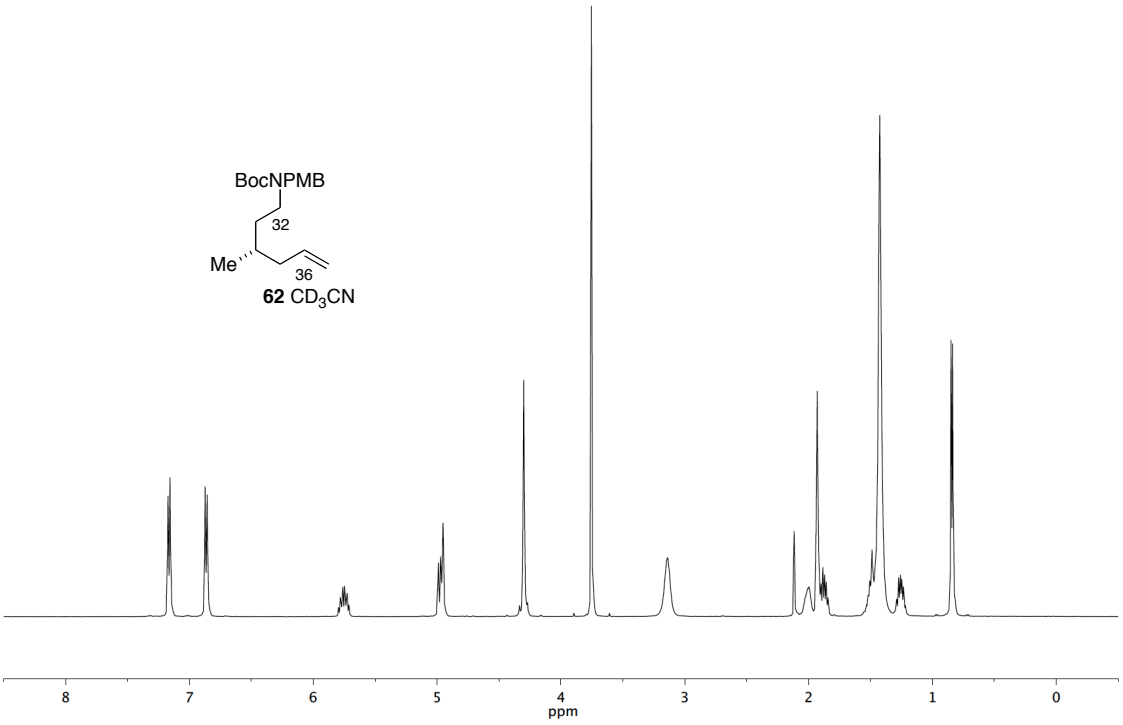

**60** $CDCl_3$

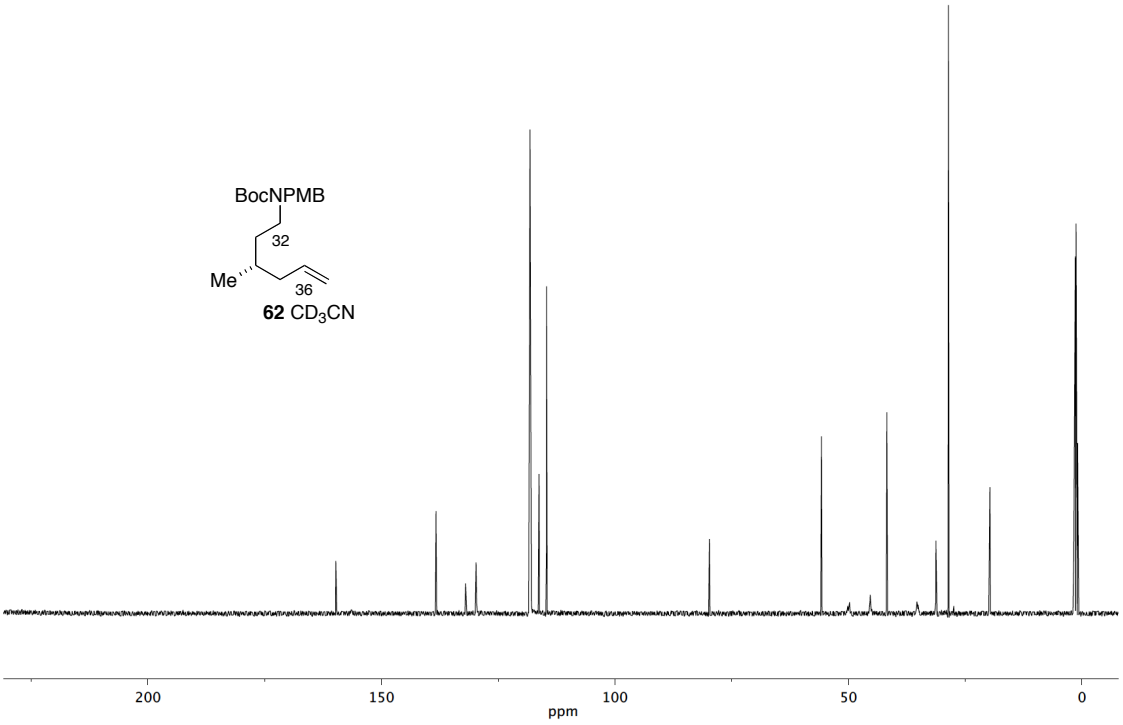


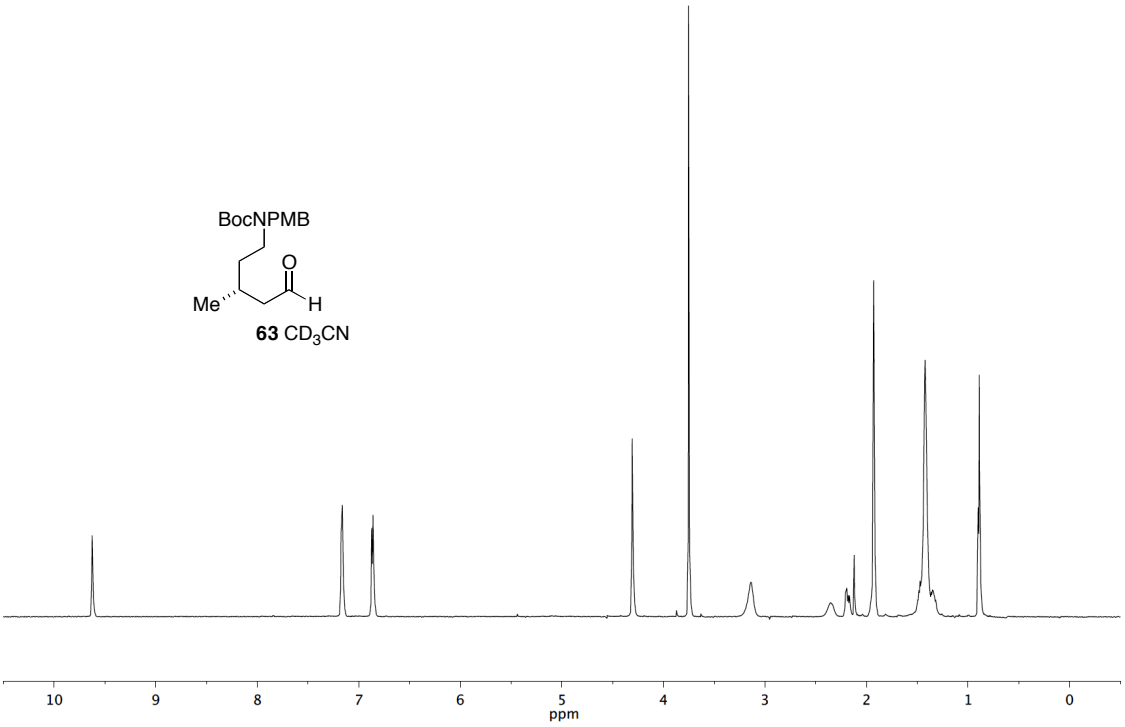

**60** $CDCl_3$

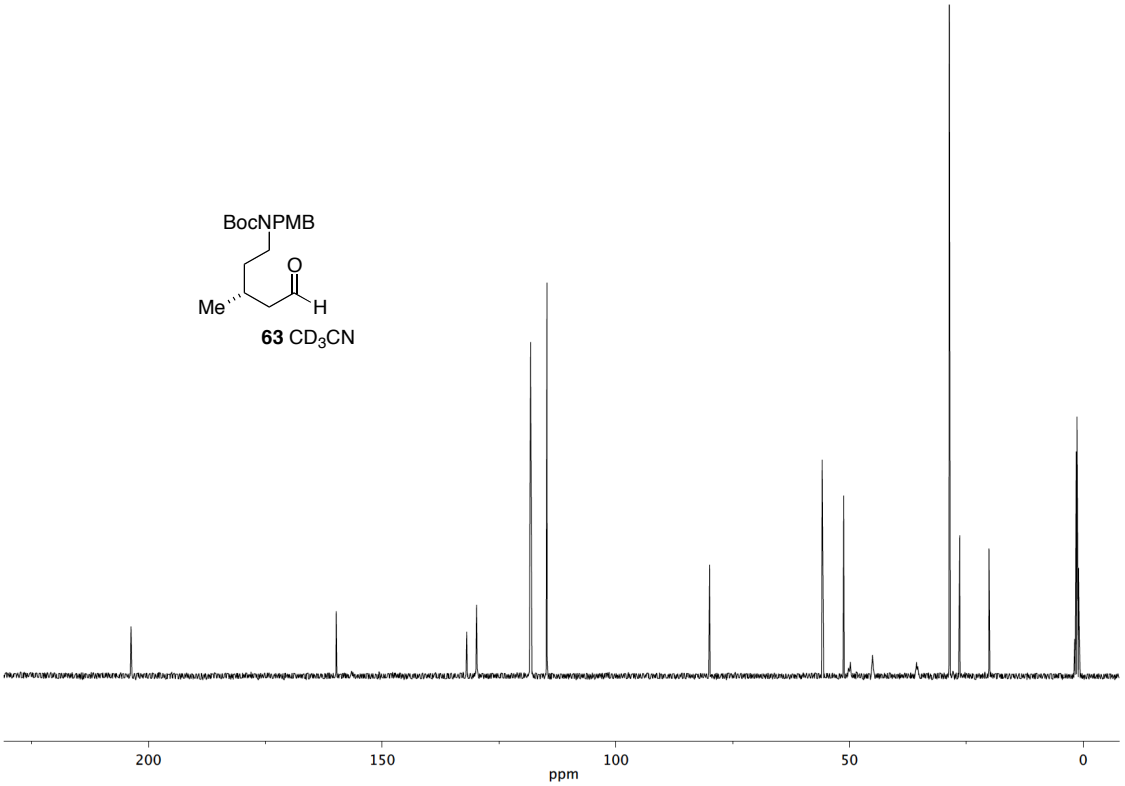

NHPMB
32
Me
36
61 CDCl3
8
7
6
5
4
3
2
1
0
ppm

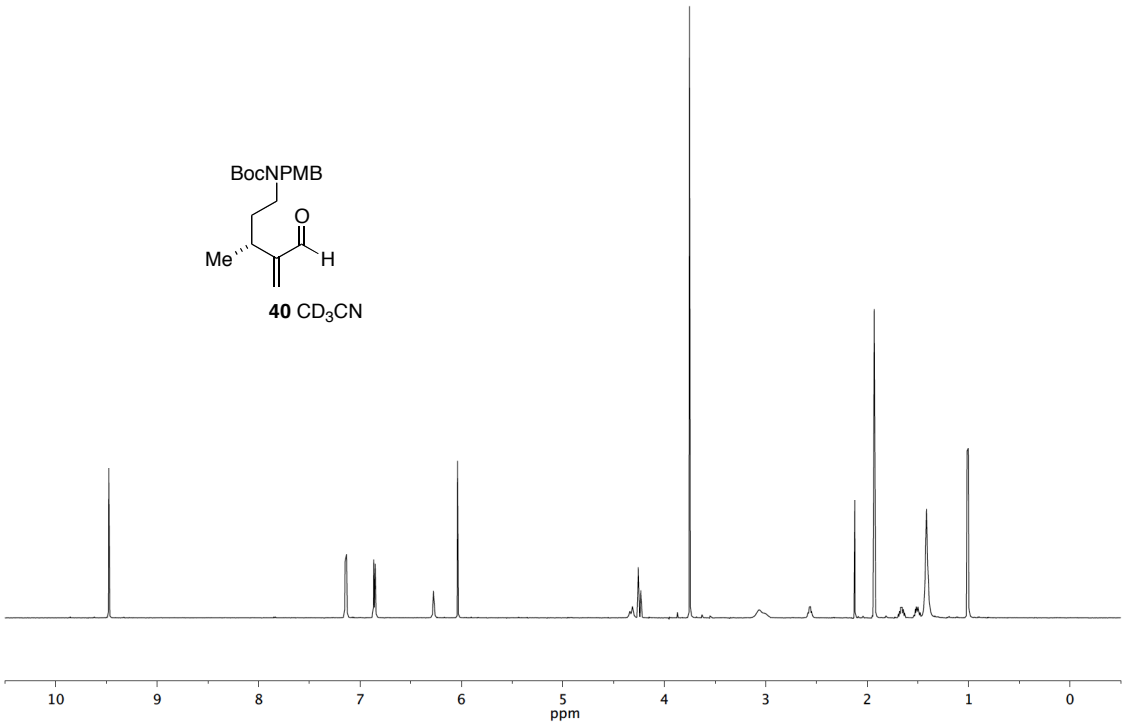

NHPMB
32
Me
36
61 CDCl3
200
150
100
50
0
ppm


BocNPMB
32
Me
36
62 CD3CN
8
7
6
5
4
3
2
1
0
ppm

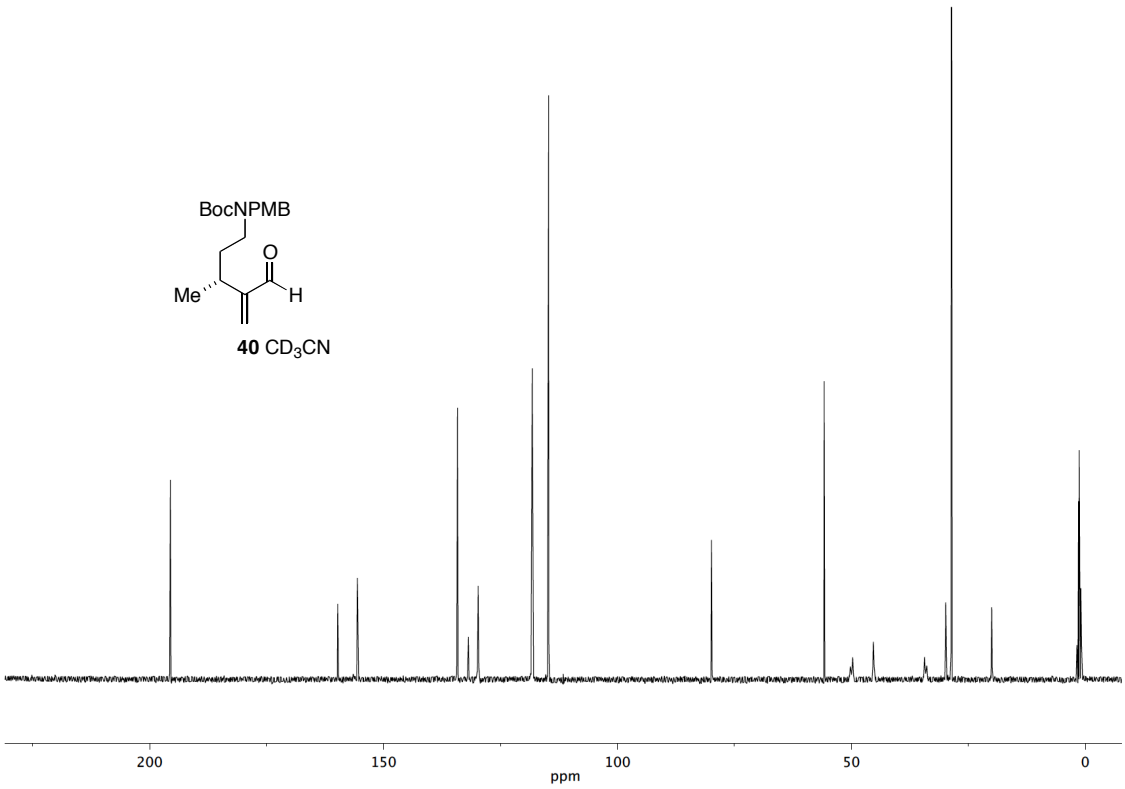

BocNPMB
32
Me
36
62 CD3CN
200
150
100
50
0
ppm


BocNPMB
O
Me
H
63 CD3CN
10
9
8
7
6
5
4
3
2
1
0
ppm

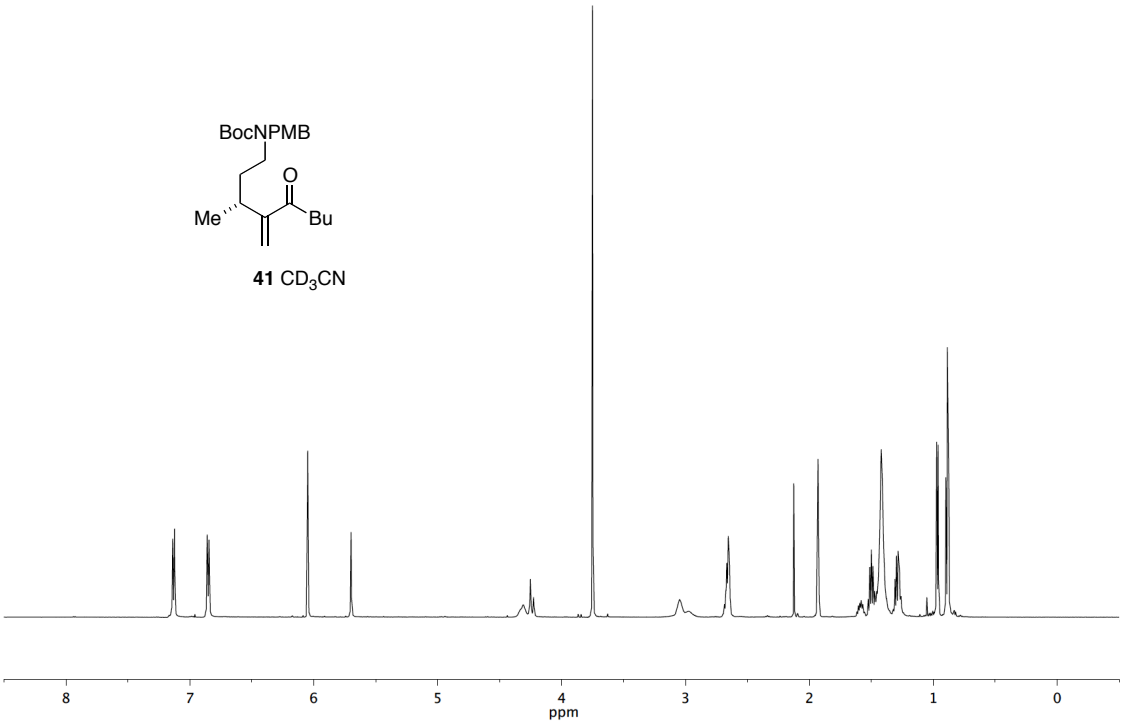

BocNPMB
O
Me
H
63 CD3CN
200
150
100
50
0
ppm



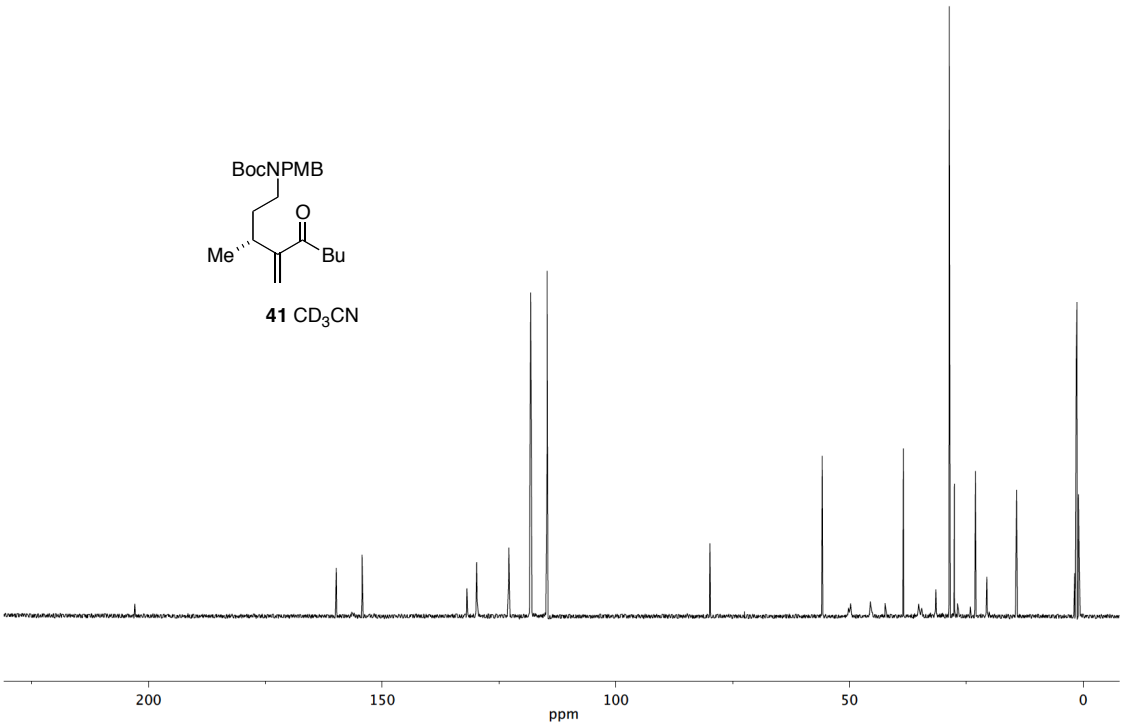

**40** $CD_3CN$



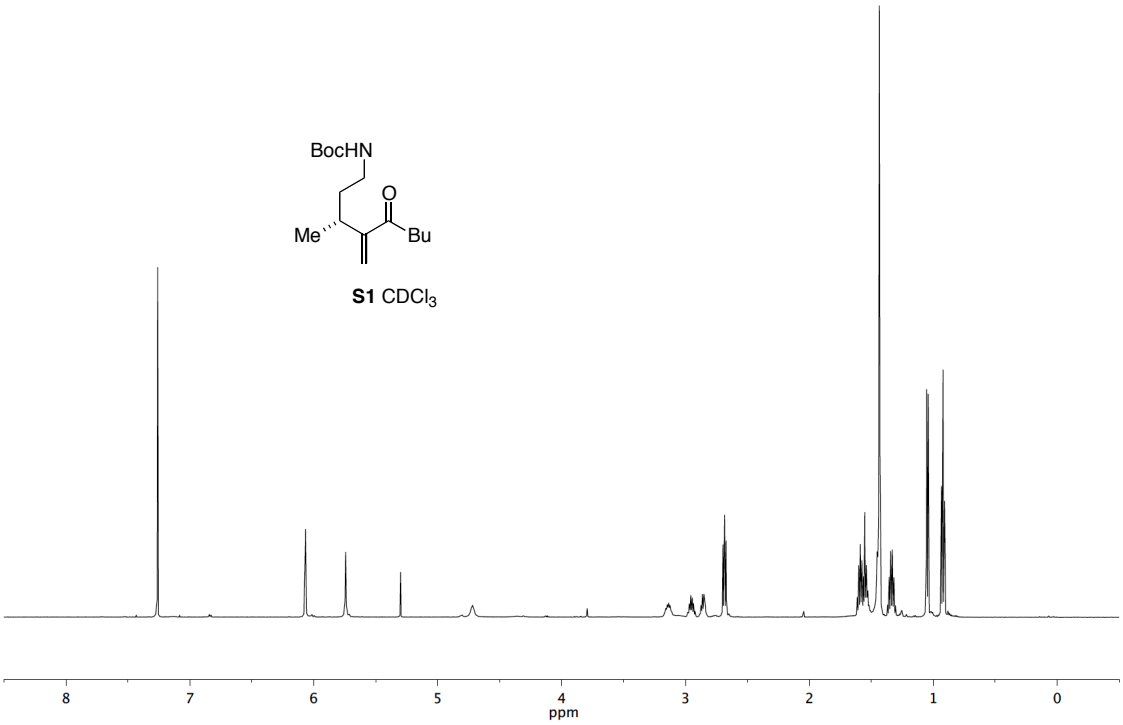

**40** $CD_3CN$



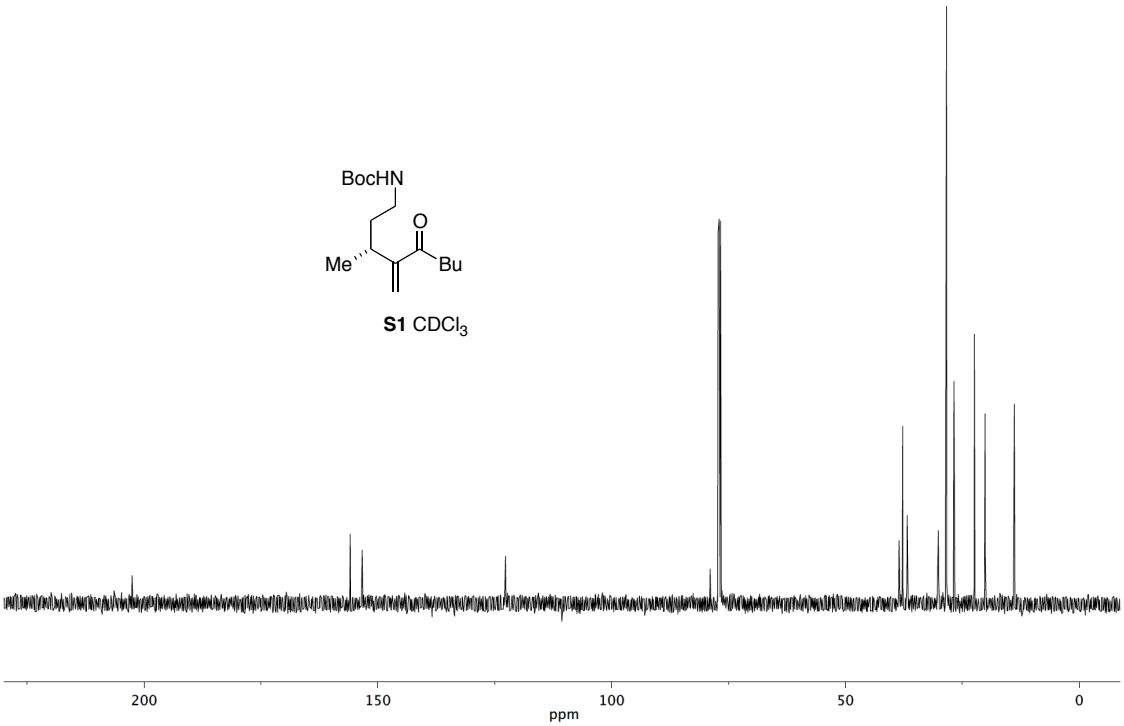

**41** $CD_3CN$



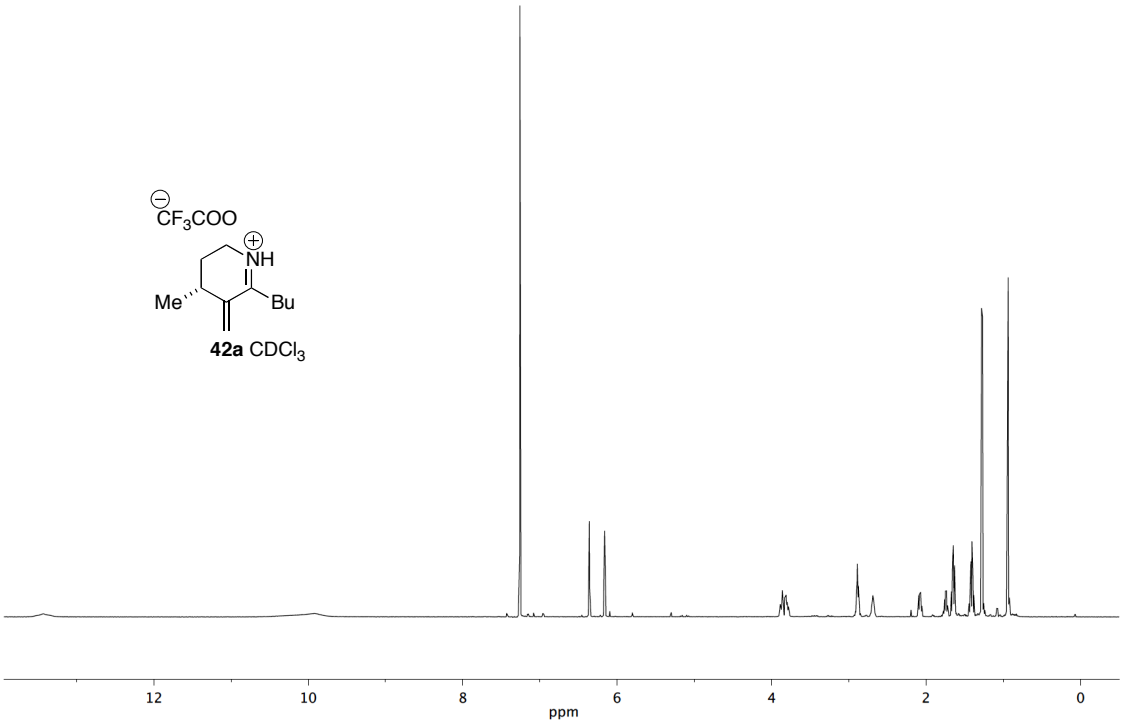

**41** $CD_3CN$

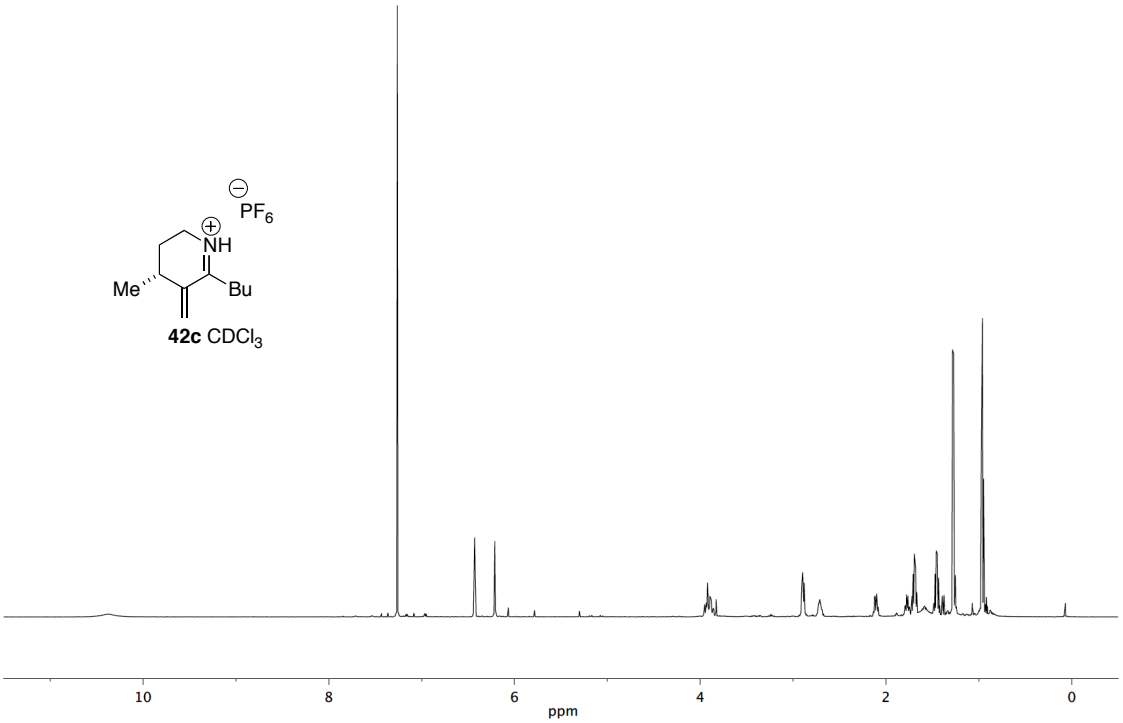


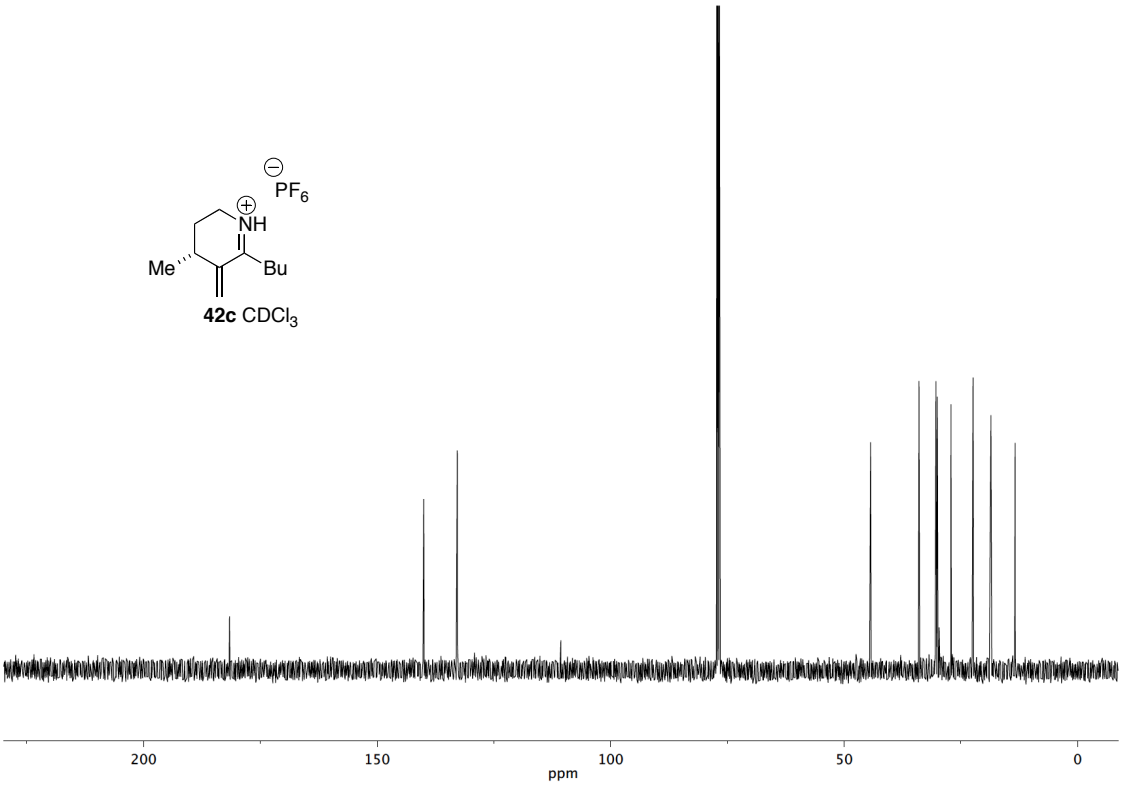

**S1** $CDCl_3$

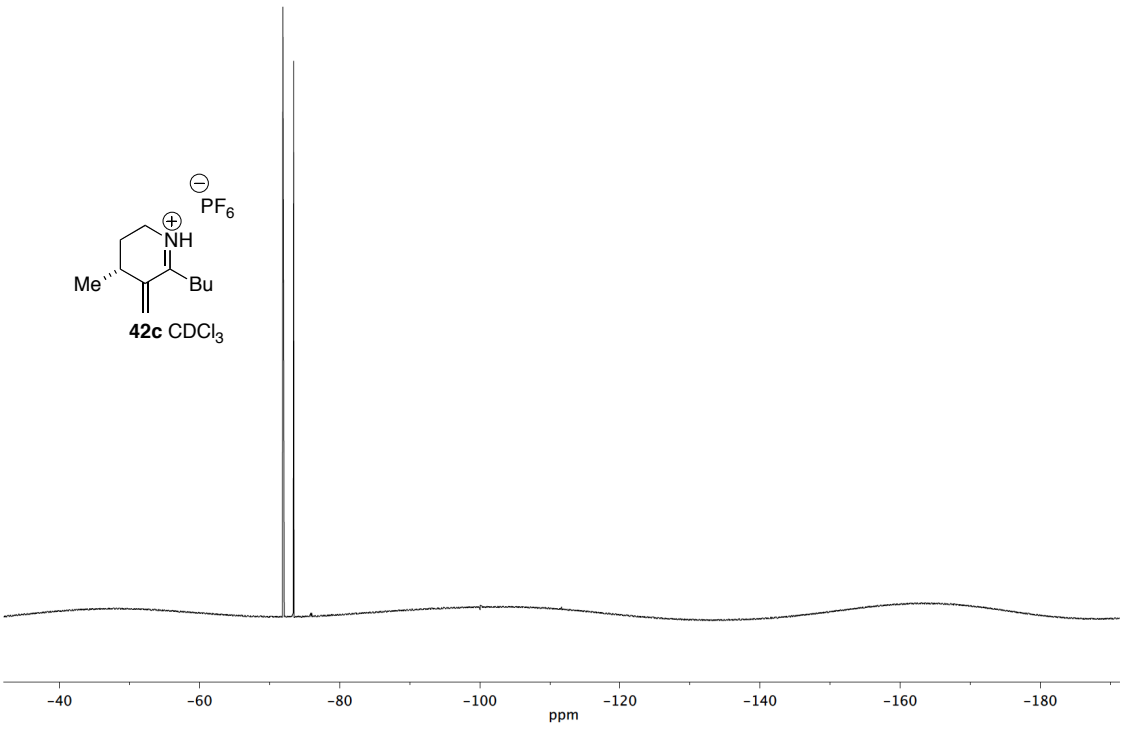


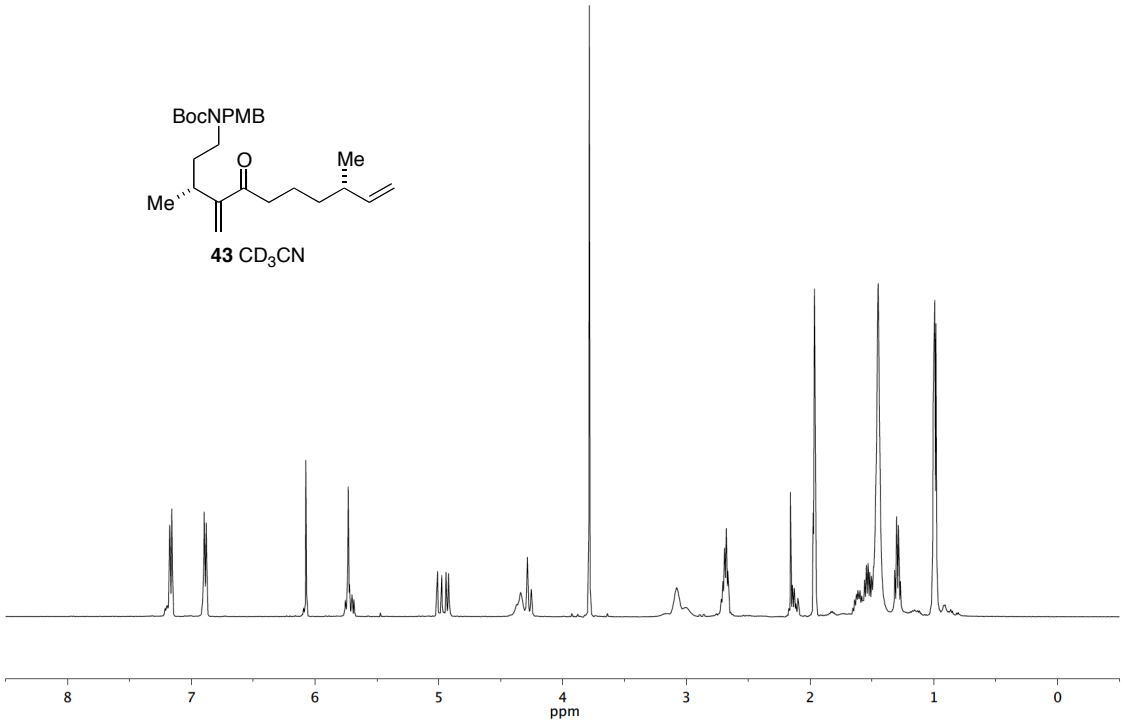

**S1** $CDCl_3$

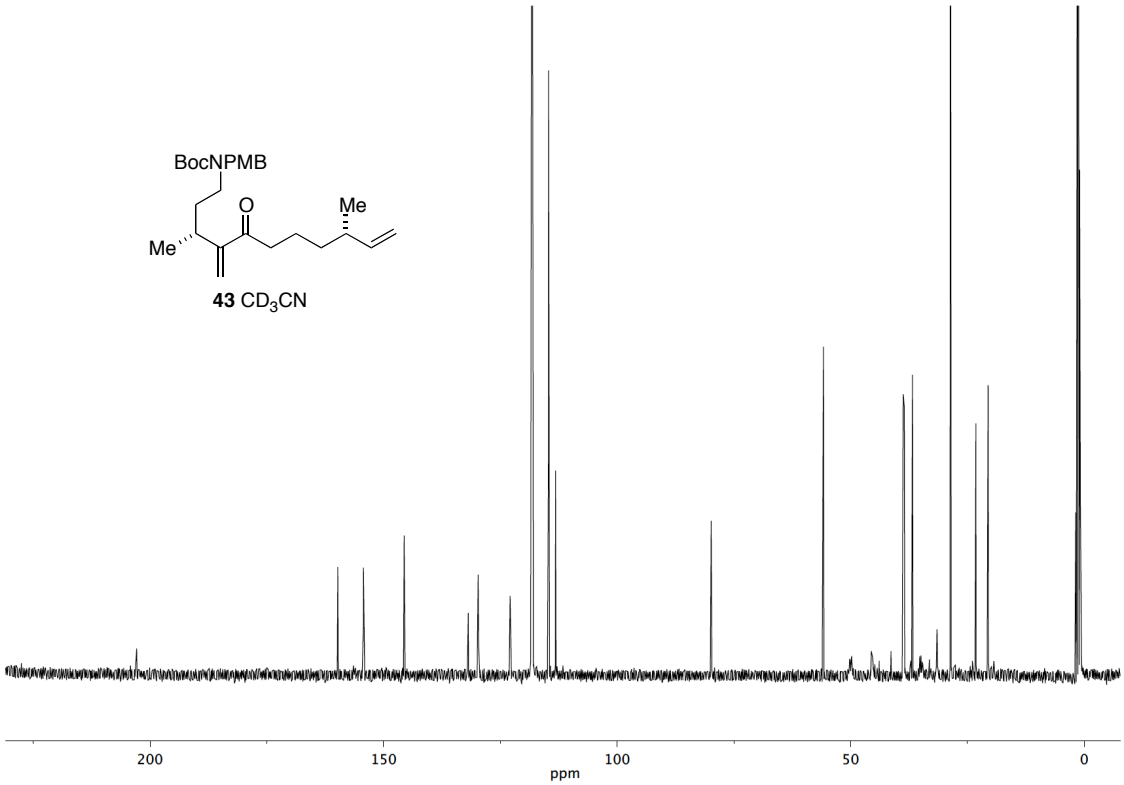

CF3COO
NH
Me
Bu
42a CDCl3
12
10
8
6
4
2
0
ppm

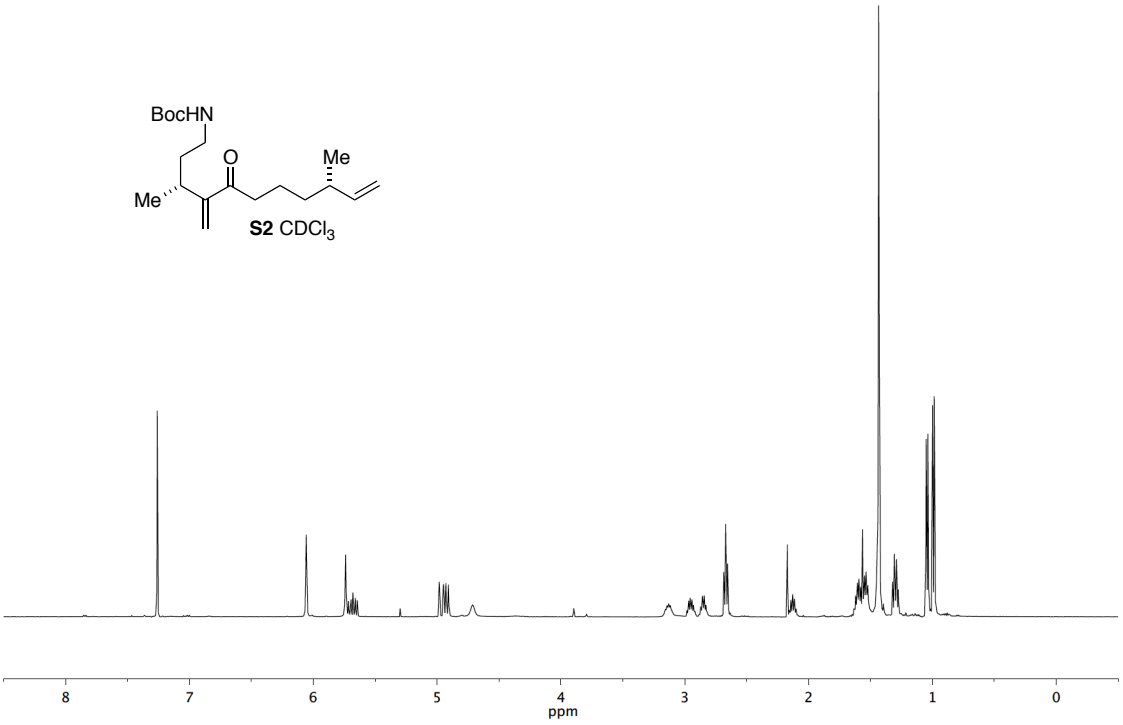

PF6
NH
Me
Bu
42c CDCl3
10
8
6
4
2
0
ppm

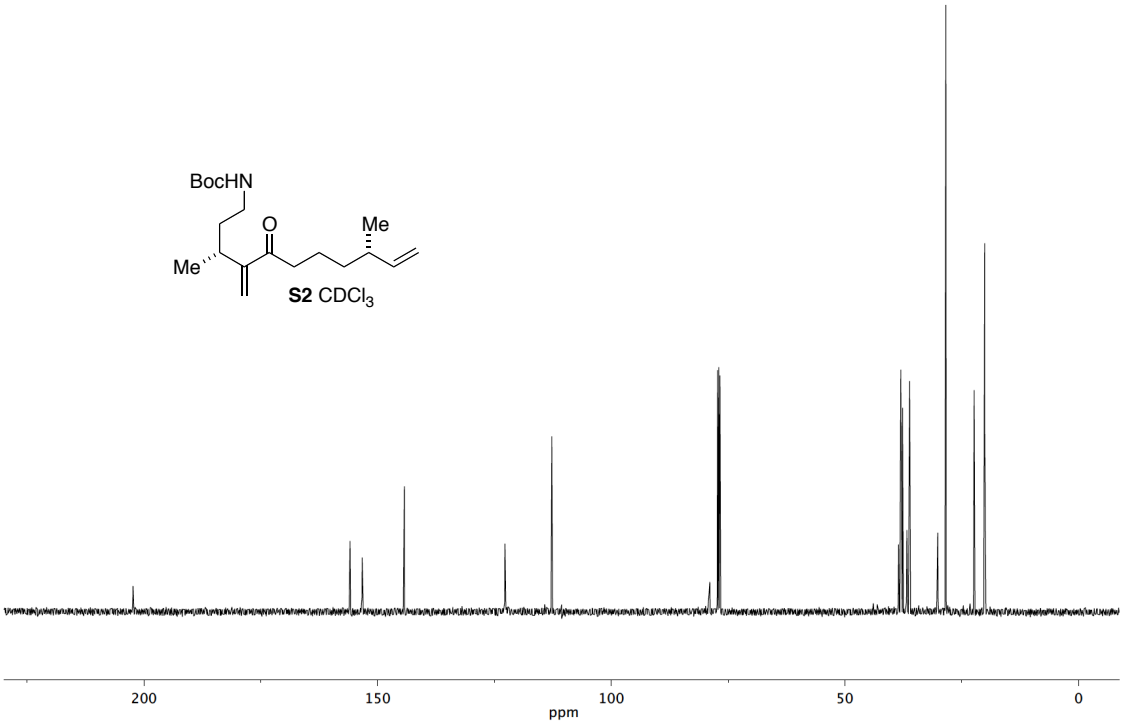

PF6
NH
Me
Bu
42c CDCl3
200
150
100
50
0
ppm

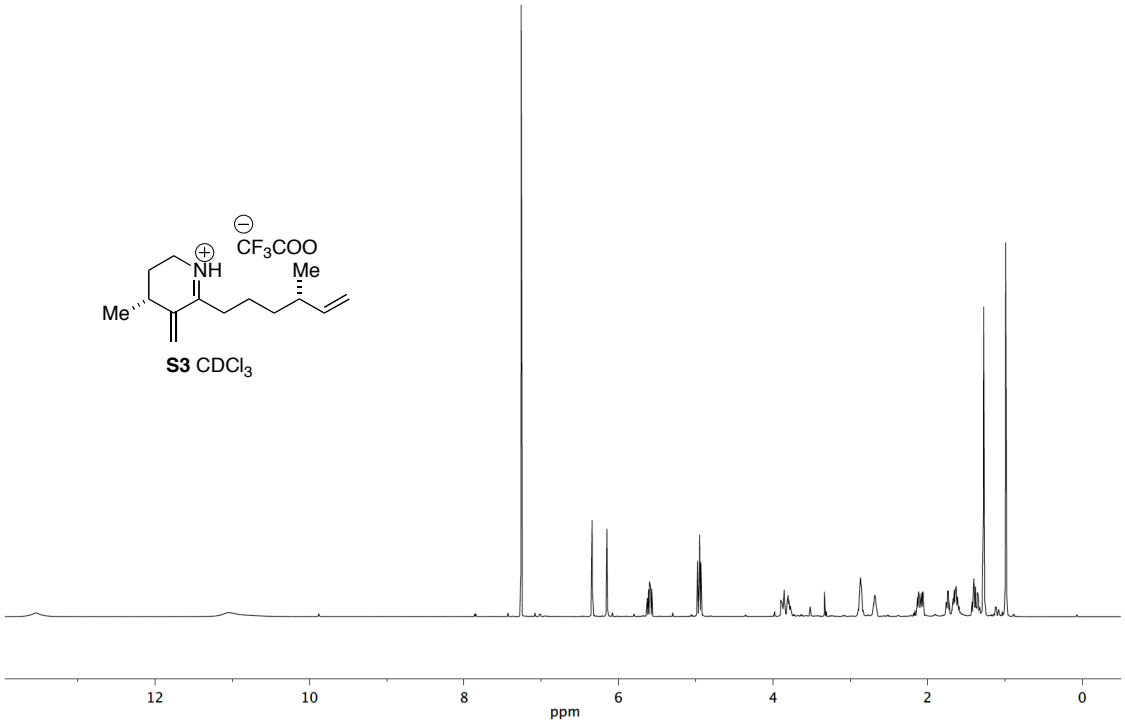

PF6
NH
Me
Bu
42c CDCl3
-40
-60
-80
-100
-120
-140
-160
-180
ppm

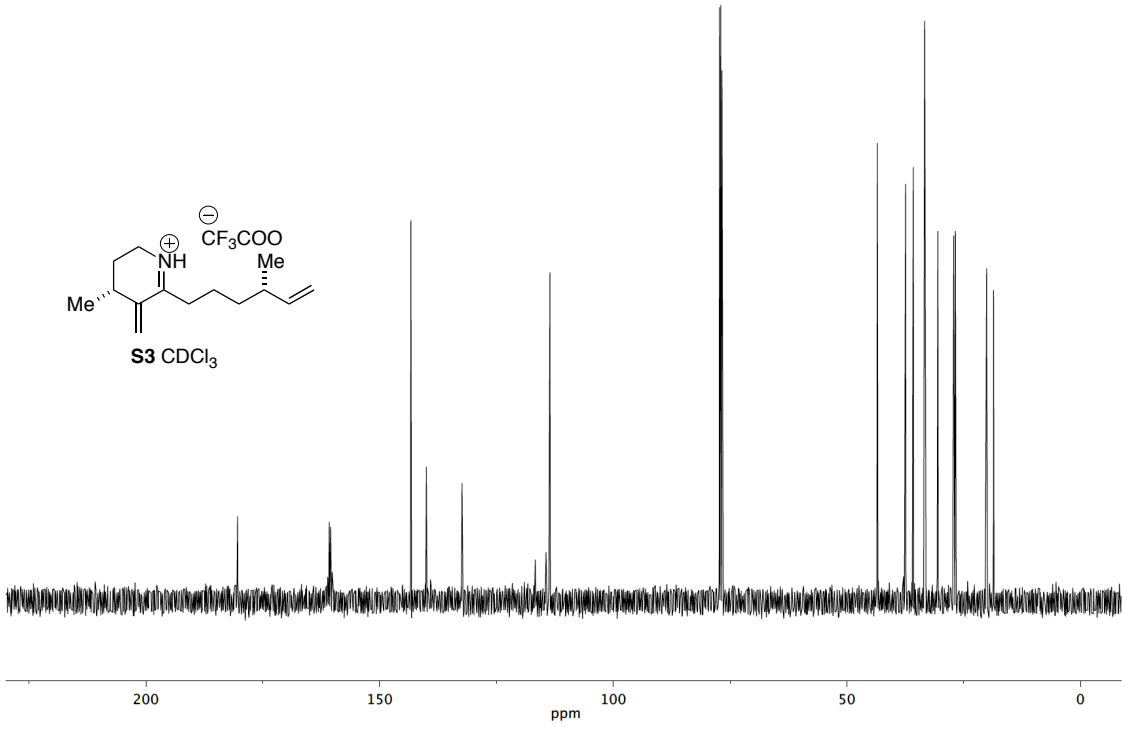

BocNPMB
O
Me
Me
43 CD3CN
8
7
6
5
4
3
2
1
0
ppm

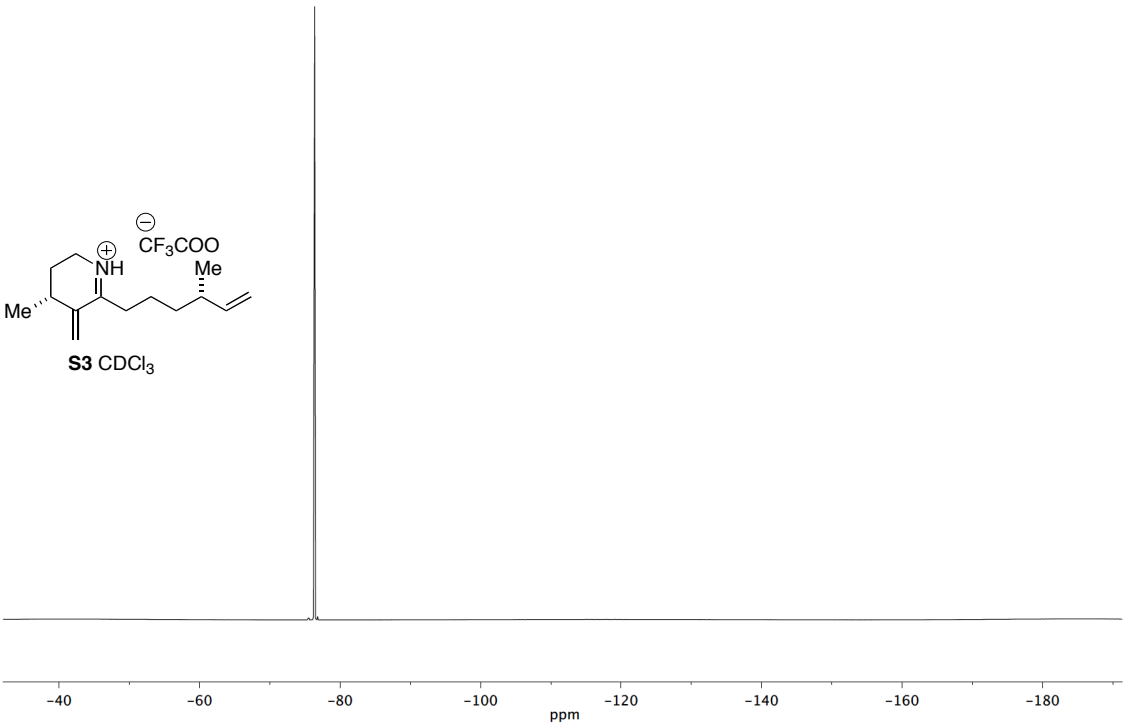

BocNPMB
O
Me
Me
43 CD3CN
200
150
100
50
0
ppm

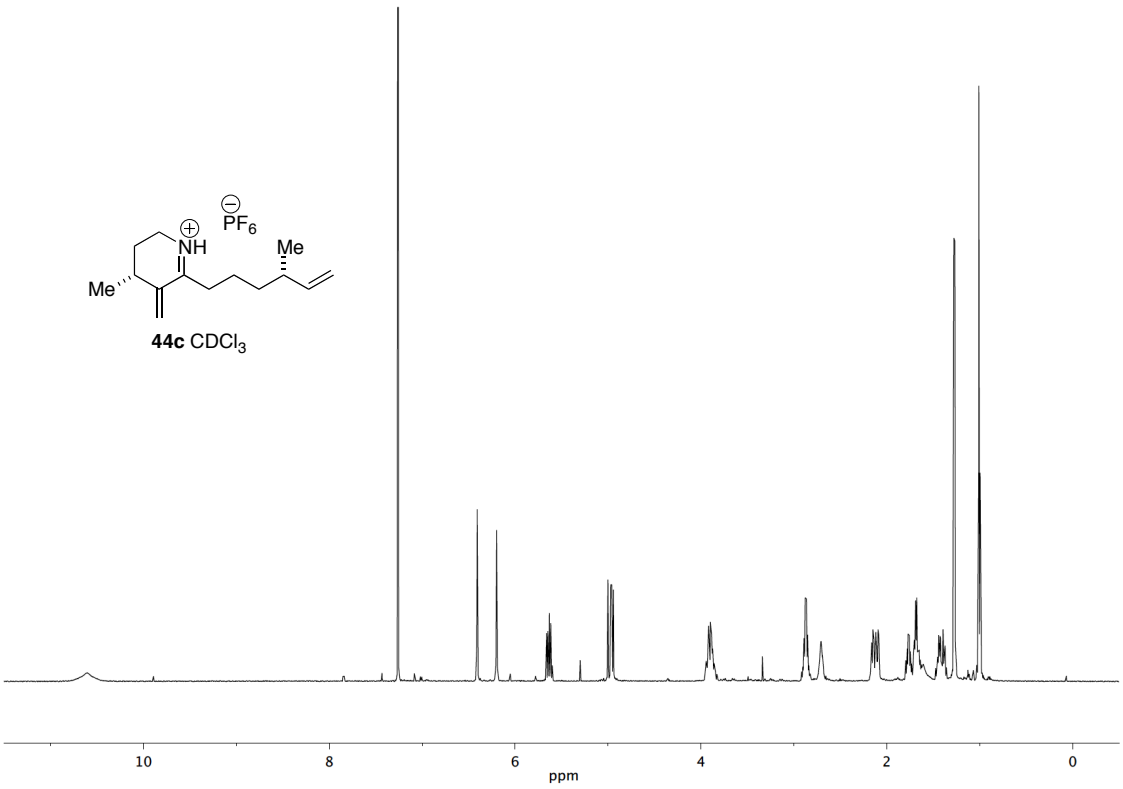

BocHN
O
Me
Me
S2 CDCl3
8
7
6
5
4
3
2
1
0
ppm

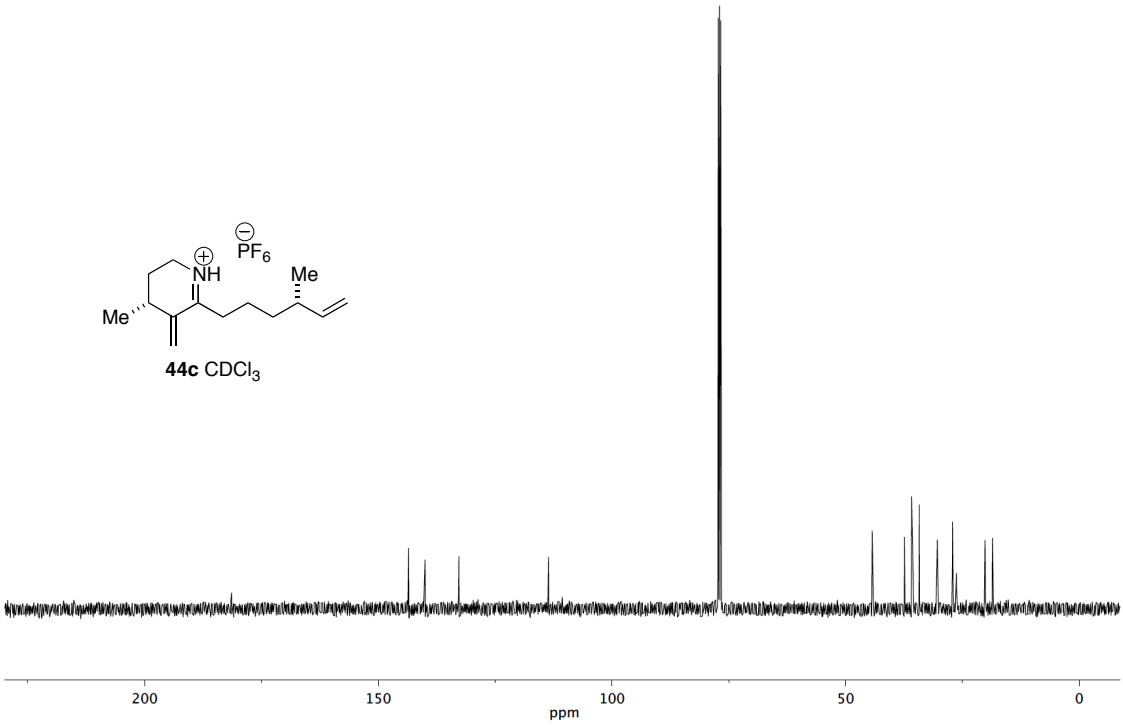

BocHN
O
Me
Me
S2 CDCl3
200
150
100
50
0
ppm

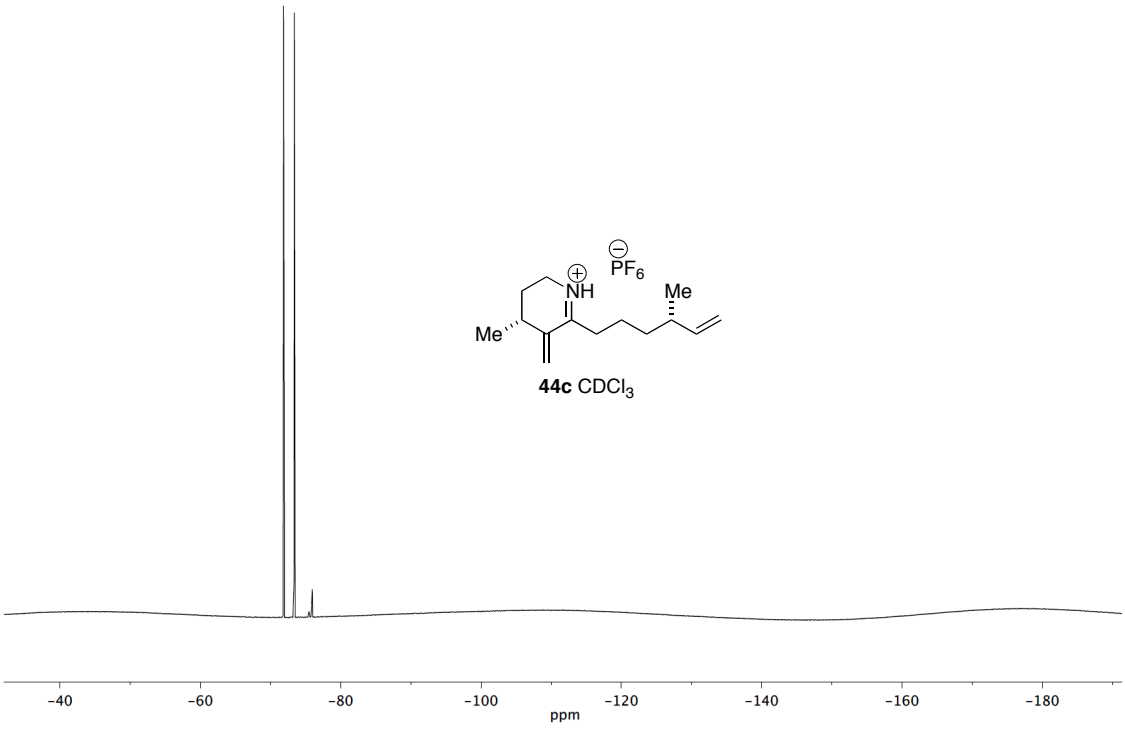

CF3COO
NH
Me
Me
S3 CDCl3
12
10
8
6
4
2
0
ppm

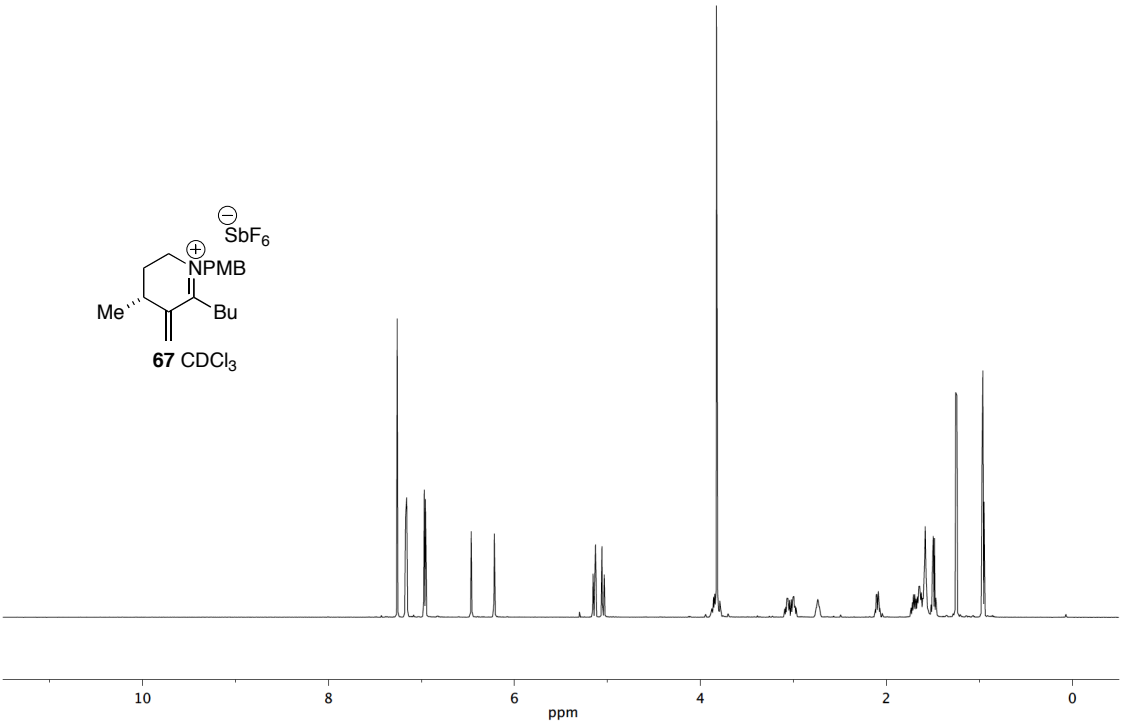

CF3COO
NH
Me
Me
S3 CDCl3
200
150
100
50
0
ppm

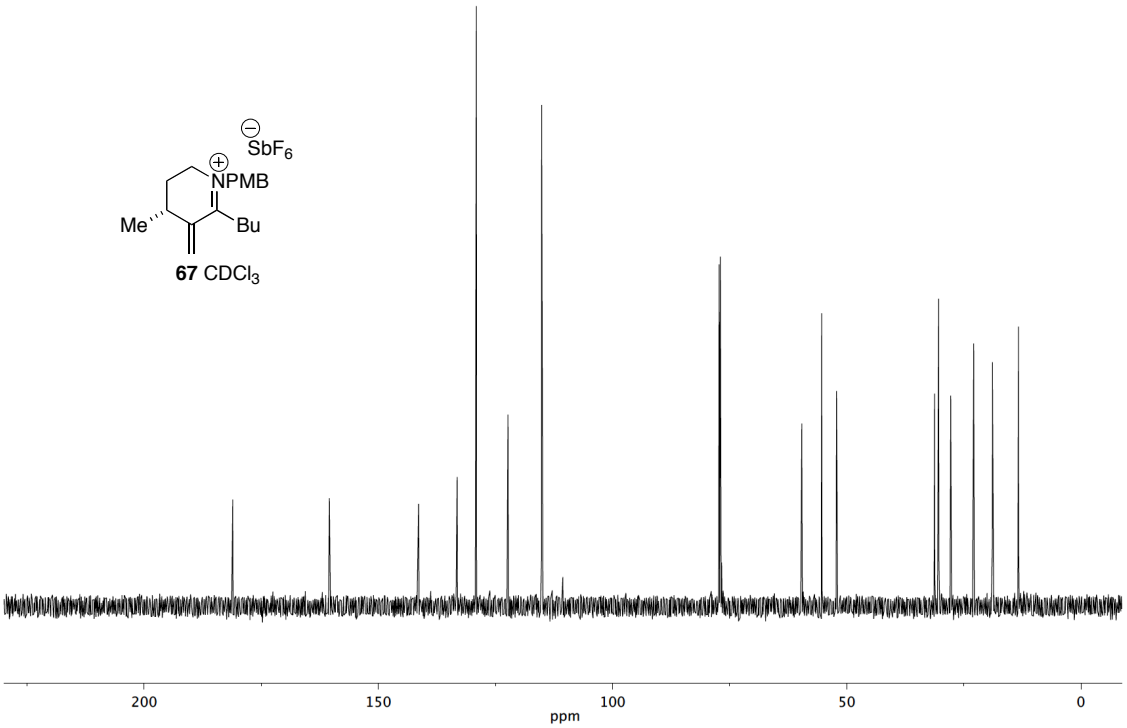

CF3COO
NH
Me
Me
S3 CDCl3
-40
-60
-80
-100
-120
-140
-160
-180
ppm


PF6
NH
Me
Me
44c CDCl3
10
8
6
4
2
0
ppm

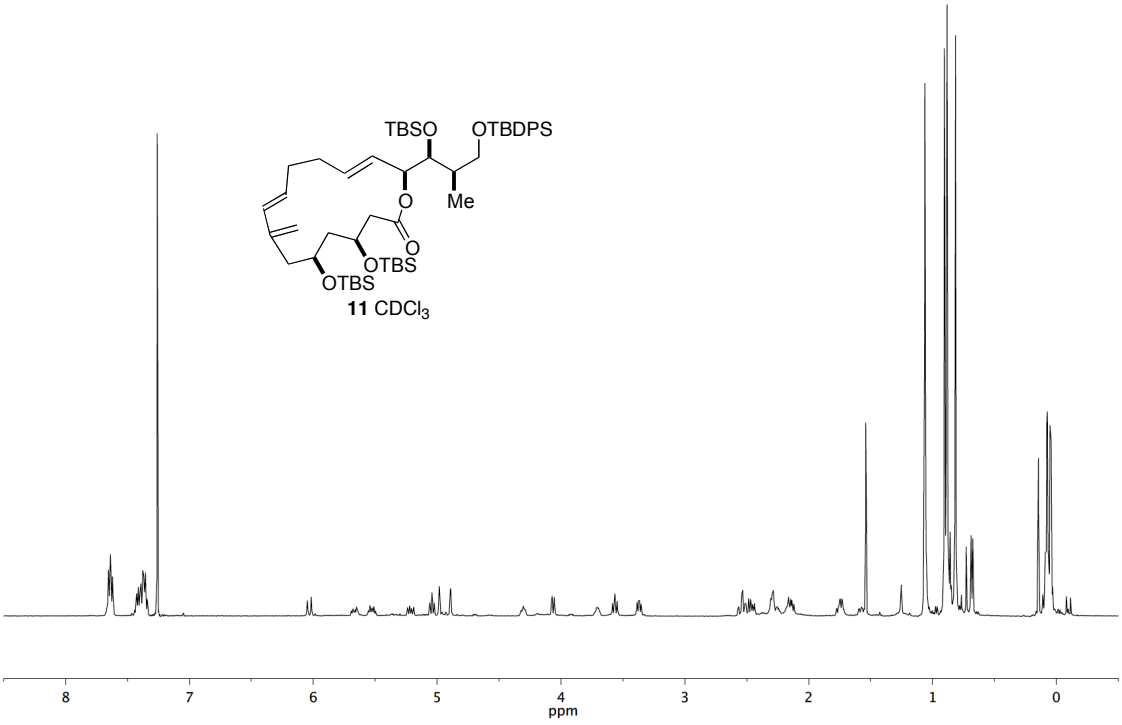

PF6
NH
Me
Me
44c CDCl3
200
150
100
50
0
ppm

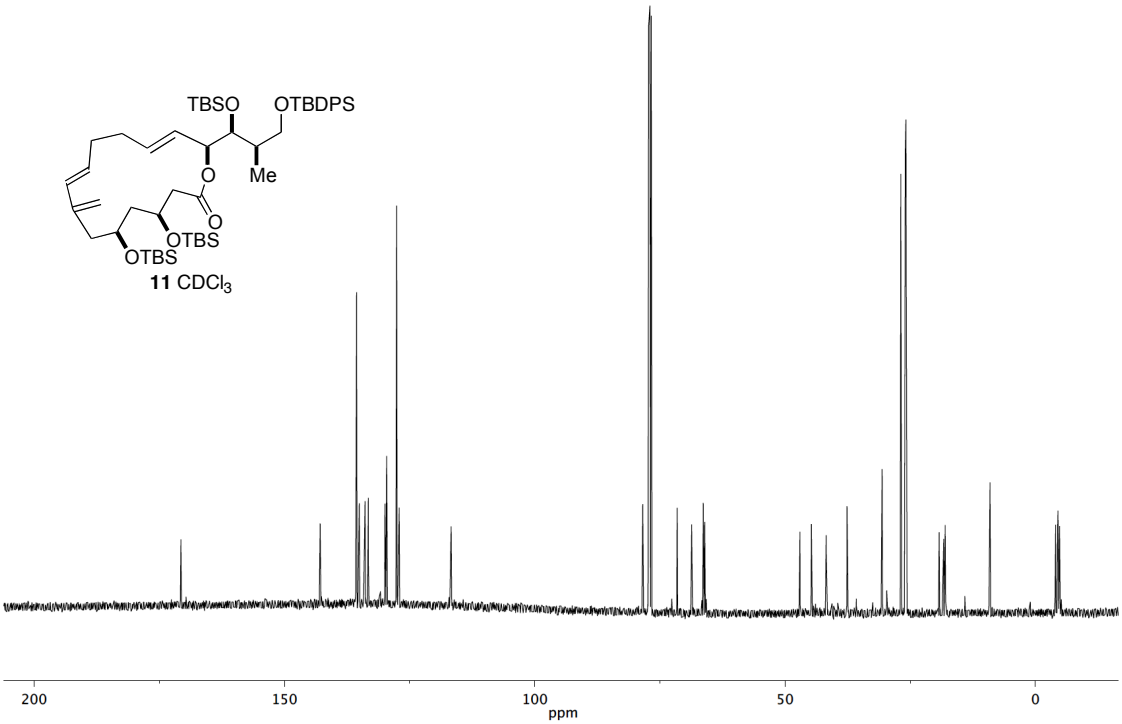

PF6
NH
Me
Me
44c CDCl3
-40
-60
-80
-100
-120
-140
-160
-180
ppm

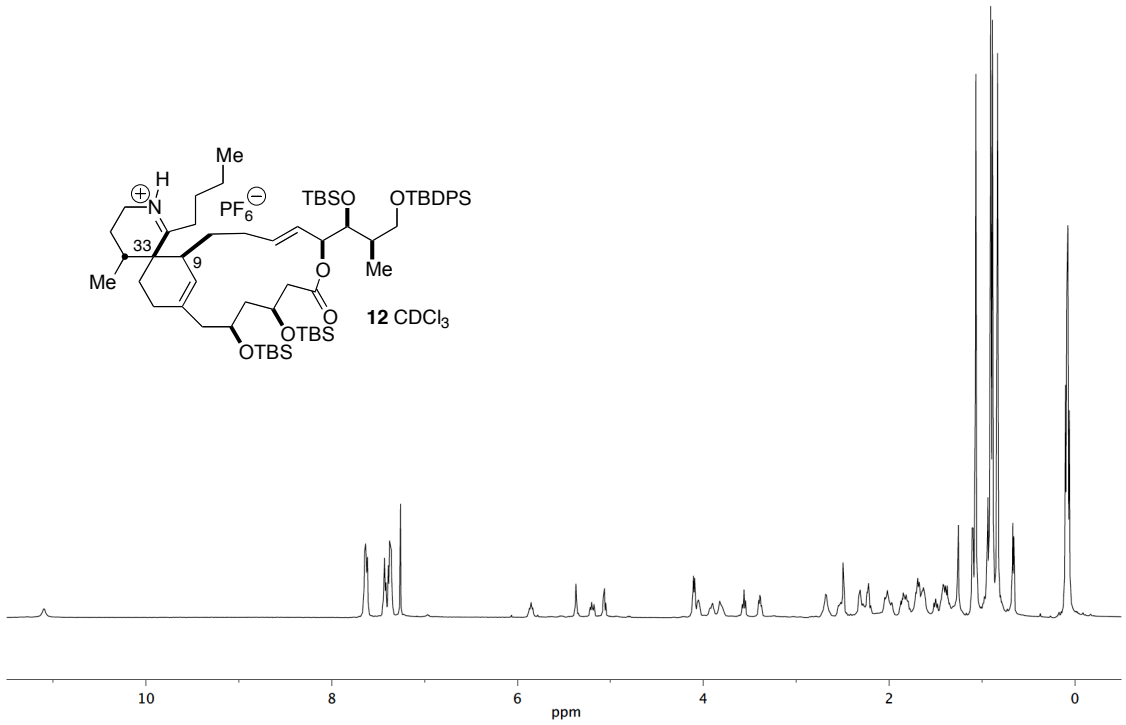

SbF6
NPMB
Me
Bu
67 CDCl3
10
8
6
4
2
0
ppm

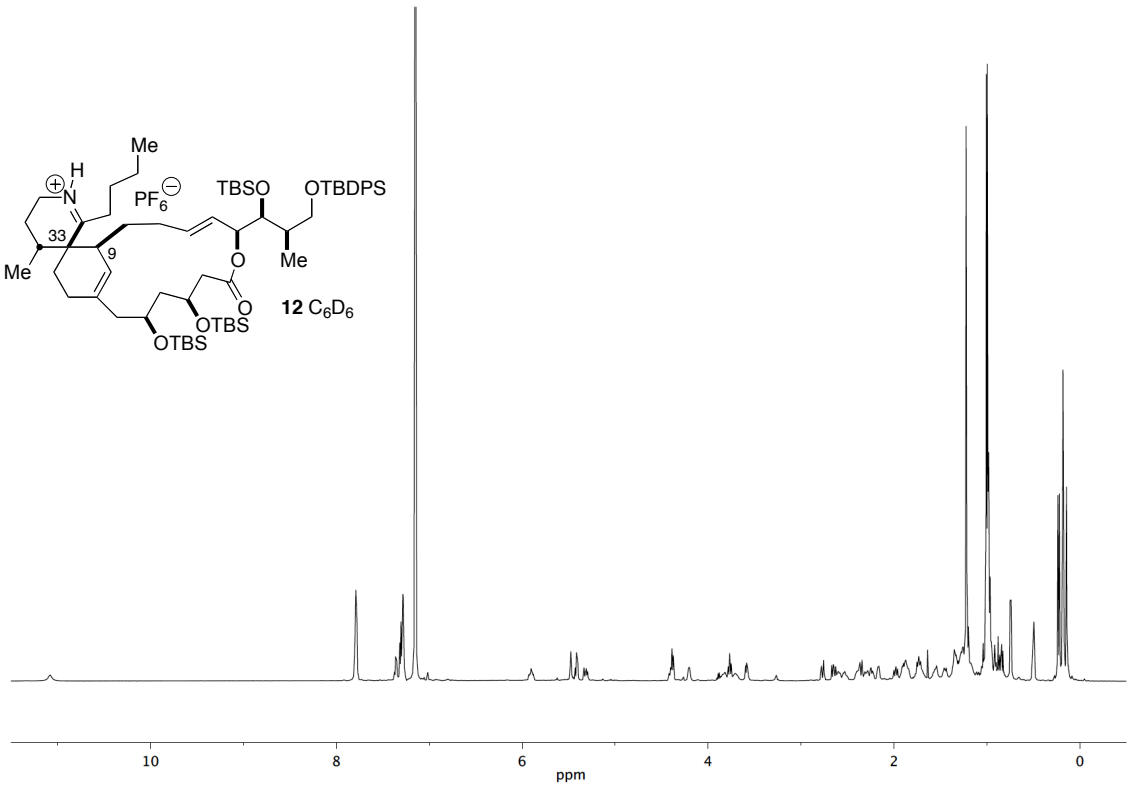

SbF6
NPMB
Me
Bu
67 CDCl3
200
150
100
50
0
ppm

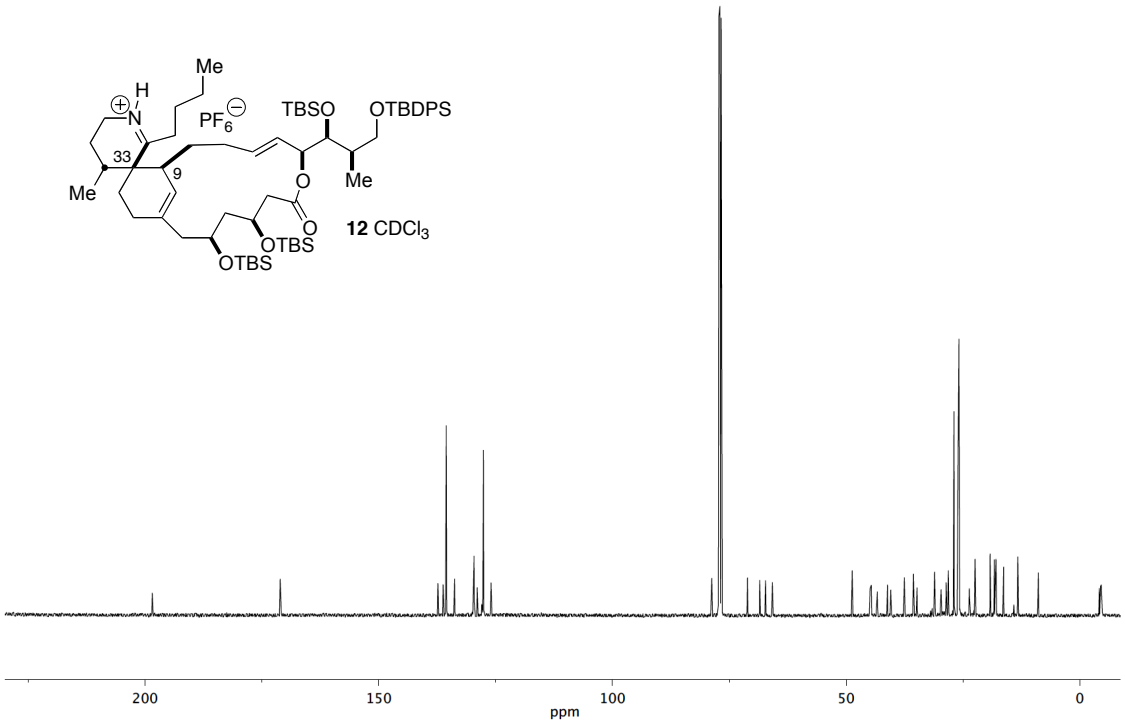
# IV. NMR Spectra from Chapter 6

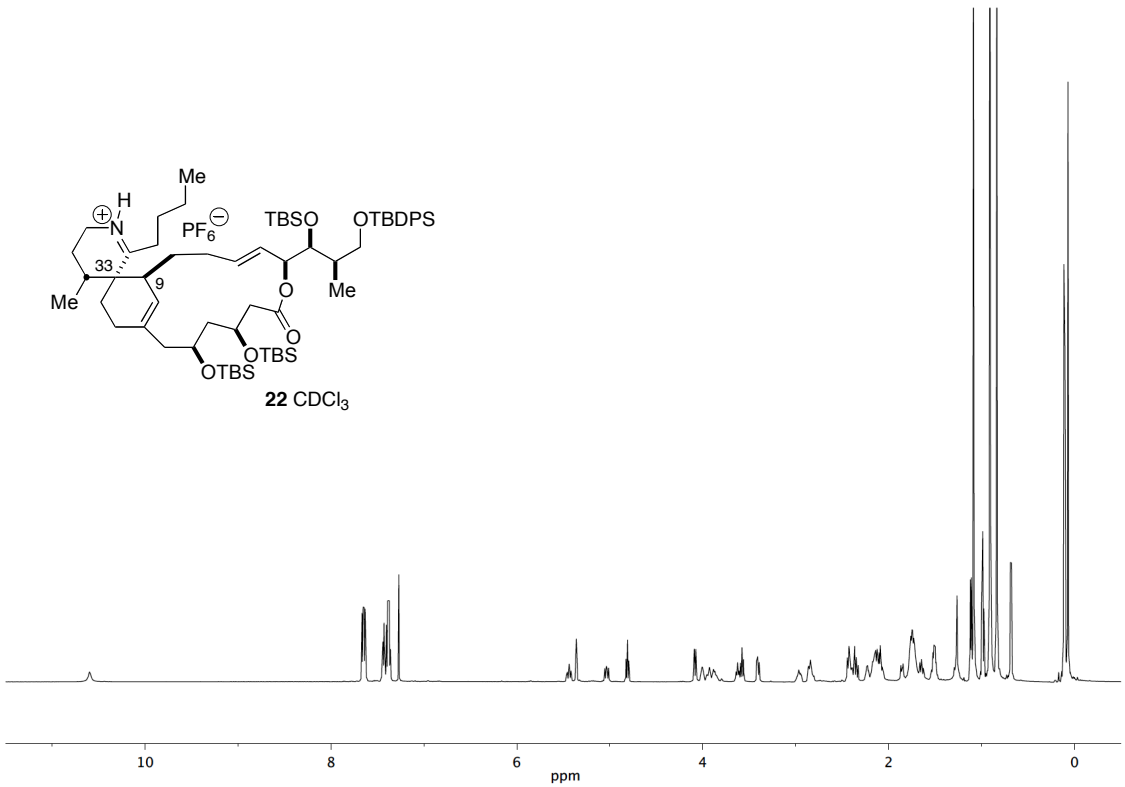


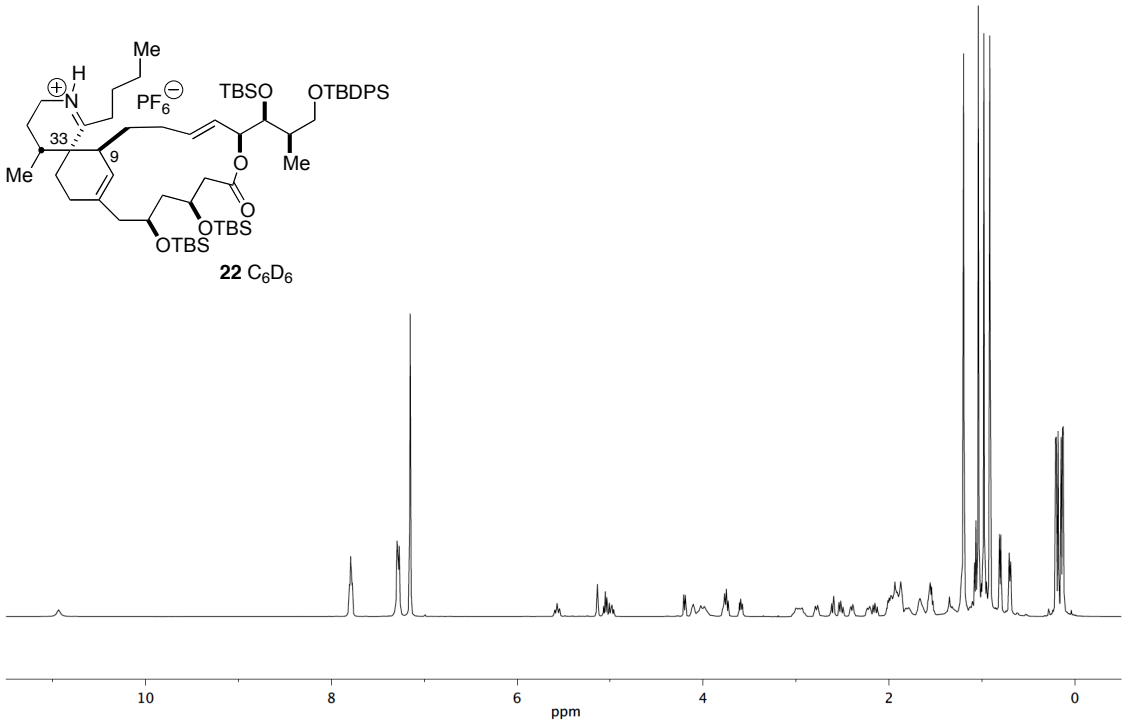




Me
H
N
PF6
TBSO
OTBDPS
33
9
Me
Me
O
O
OTBS
OTBS
12 CDCl3
10
8
6
4
2
0
ppm

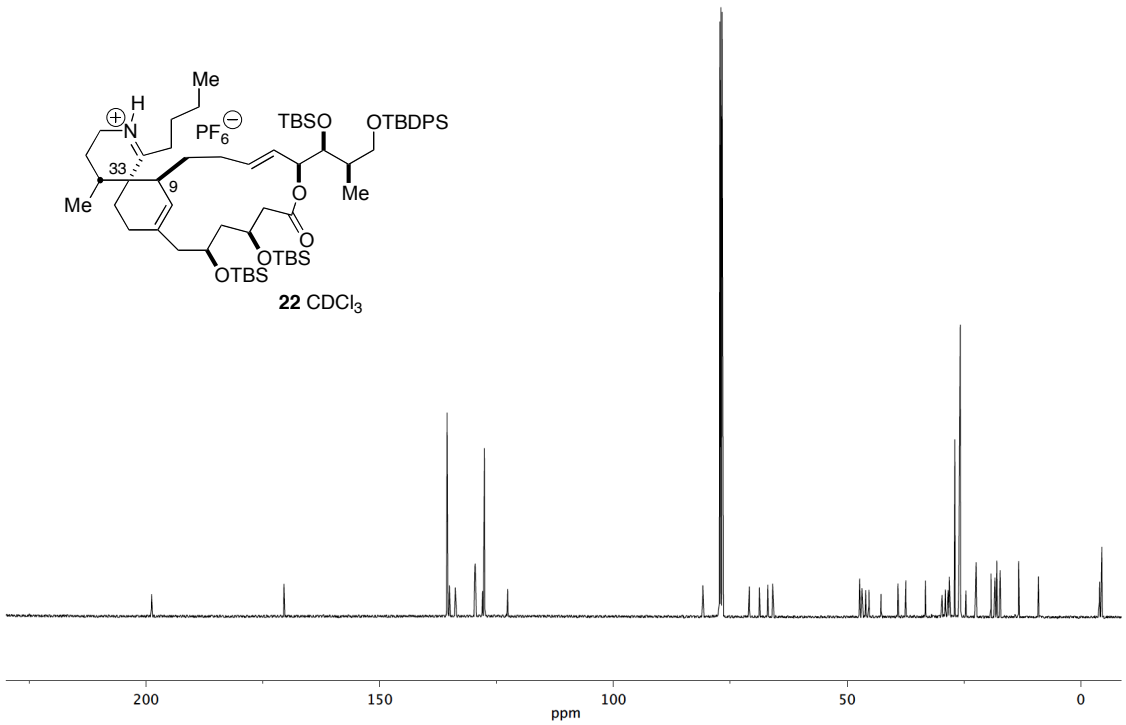

Me
H
N
PF6
TBSO
OTBDPS
33
9
Me
Me
O
O
OTBS
OTBS
12 C6D6
10
8
6
4
2
0
ppm


Me
H
N
PF6
TBSO
OTBDPS
33
9
Me
O
Me
O
OTBS
OTBS
12 CDCl3
200
150
100
50
0
ppm

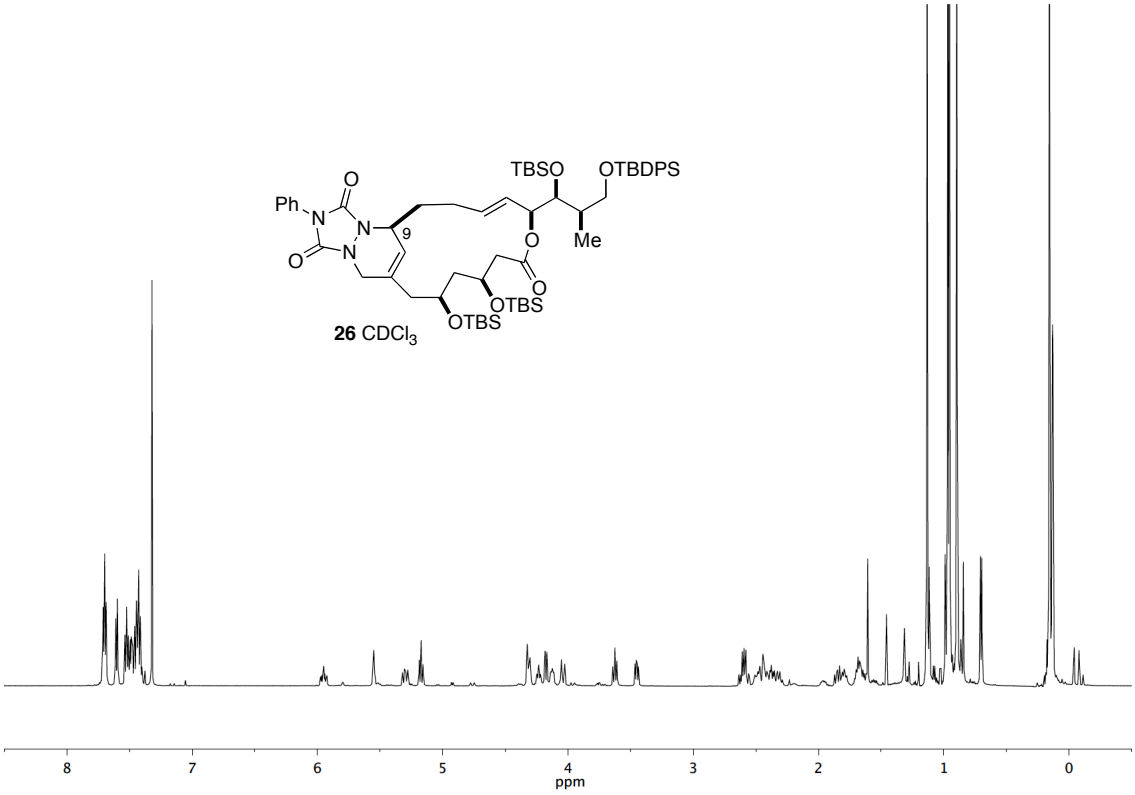

Me
H
N
PF6
TBSO
OTBDPS
33
9
Me
O
Me
O
OTBS
OTBS
22 CDCl3
10
8
6
4
2
0
ppm

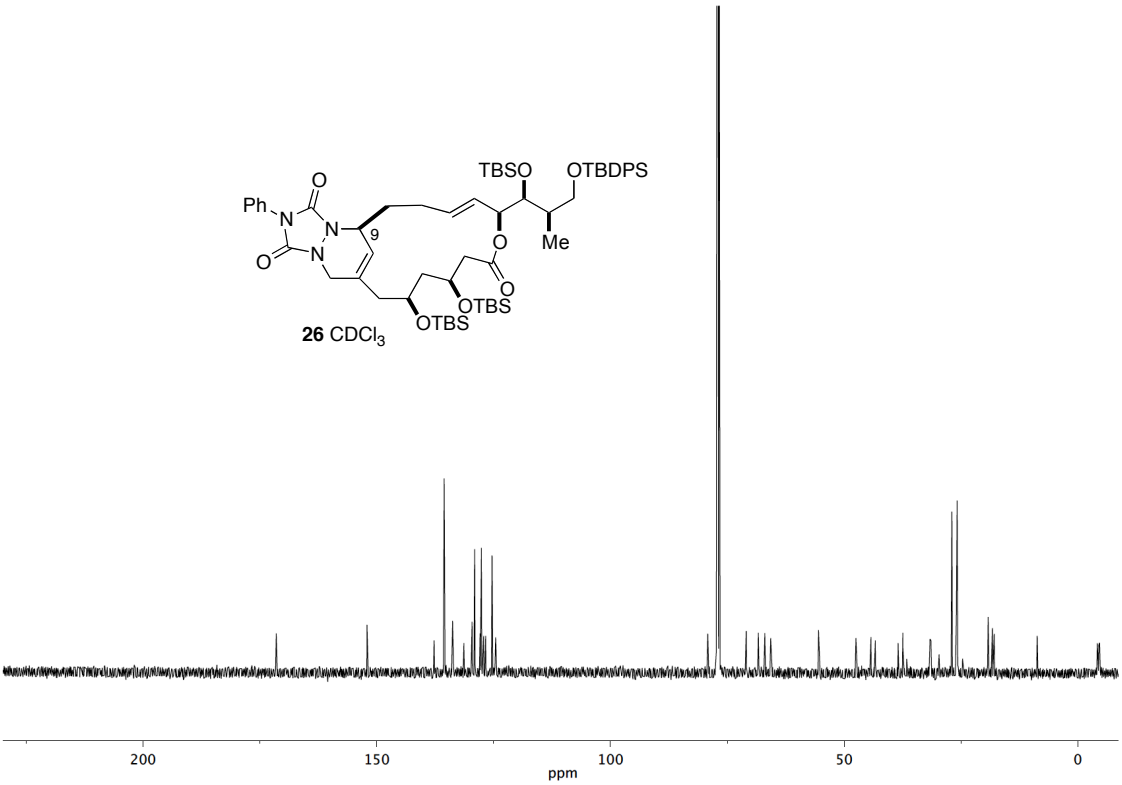


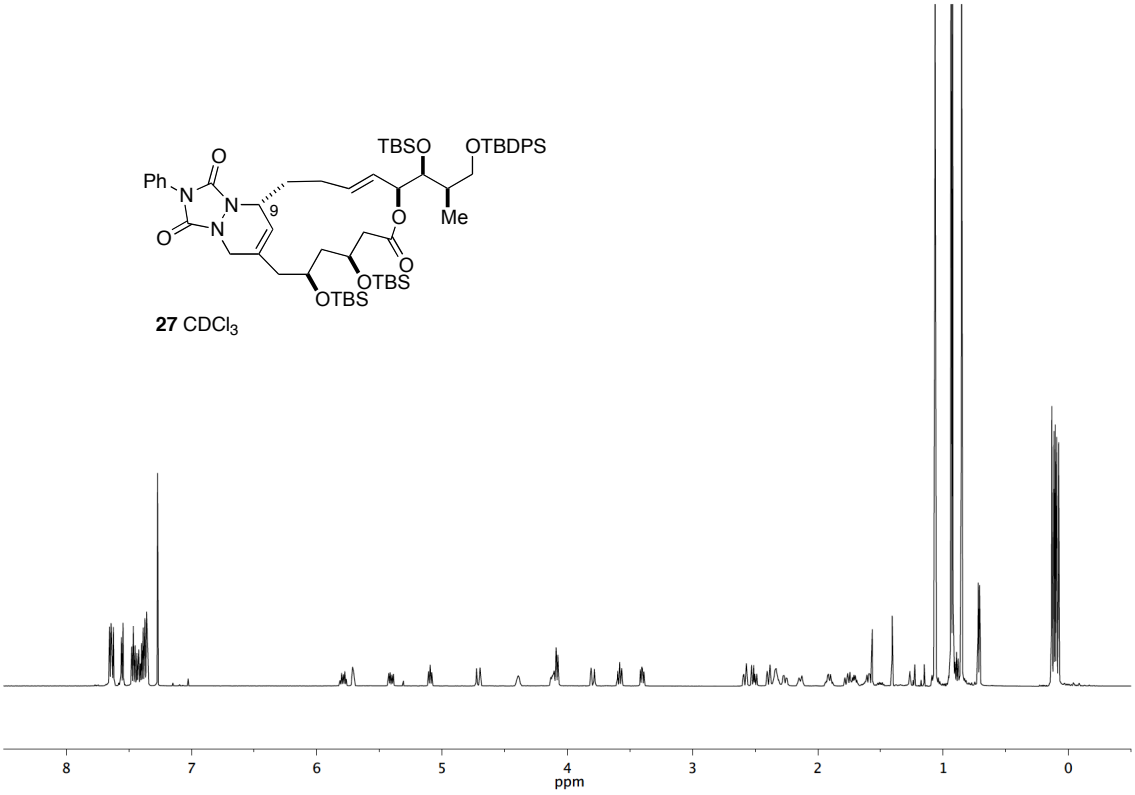

**22** $C_6D_6$



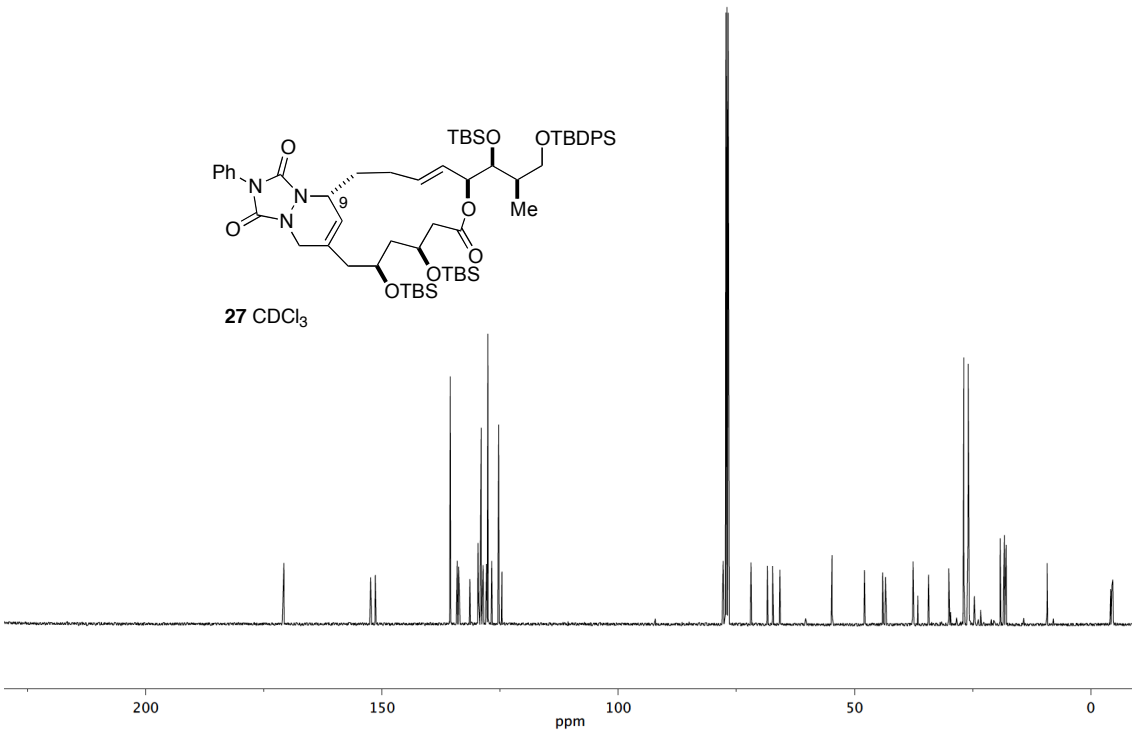

**22** $CDCl_3$


TBSO
OTBDPS
Ph
N
N
N
O
O
O
9
Me
O
O
OTBS
OTBS
26 CDCl3
8
7
6
5
4
3
2
1
0
ppm

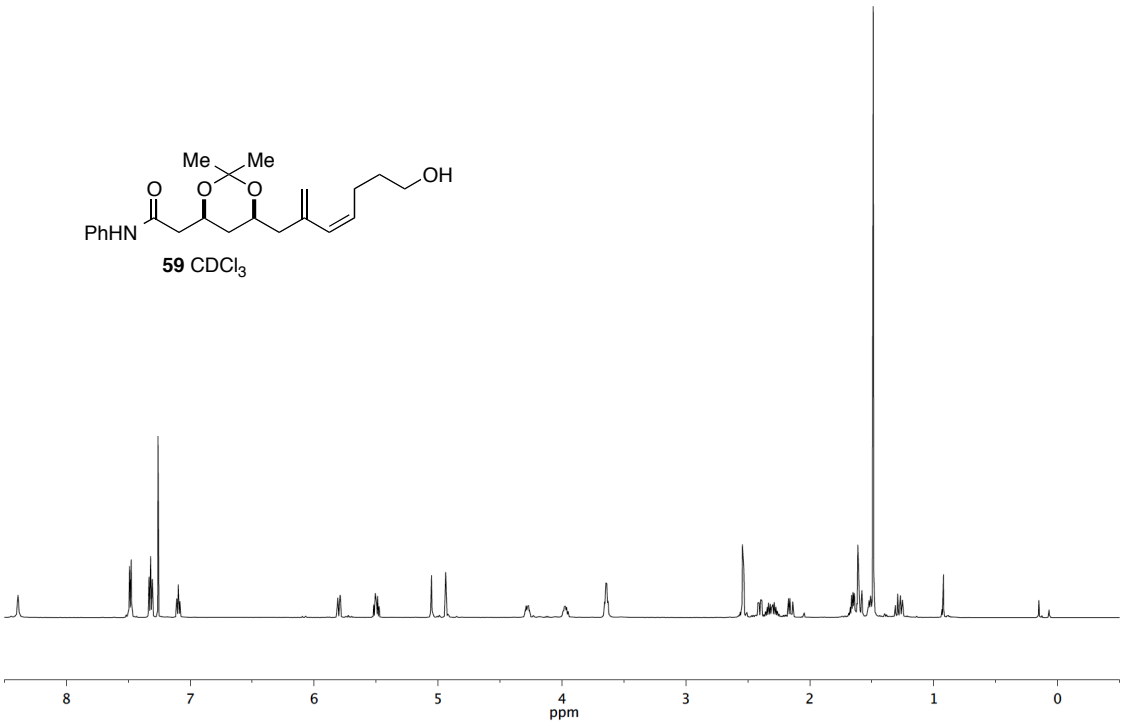

TBSO
OTBDPS
Ph
N
N
N
O
O
O
9
Me
O
O
OTBS
OTBS
26 CDCl3
200
150
100
50
0
ppm



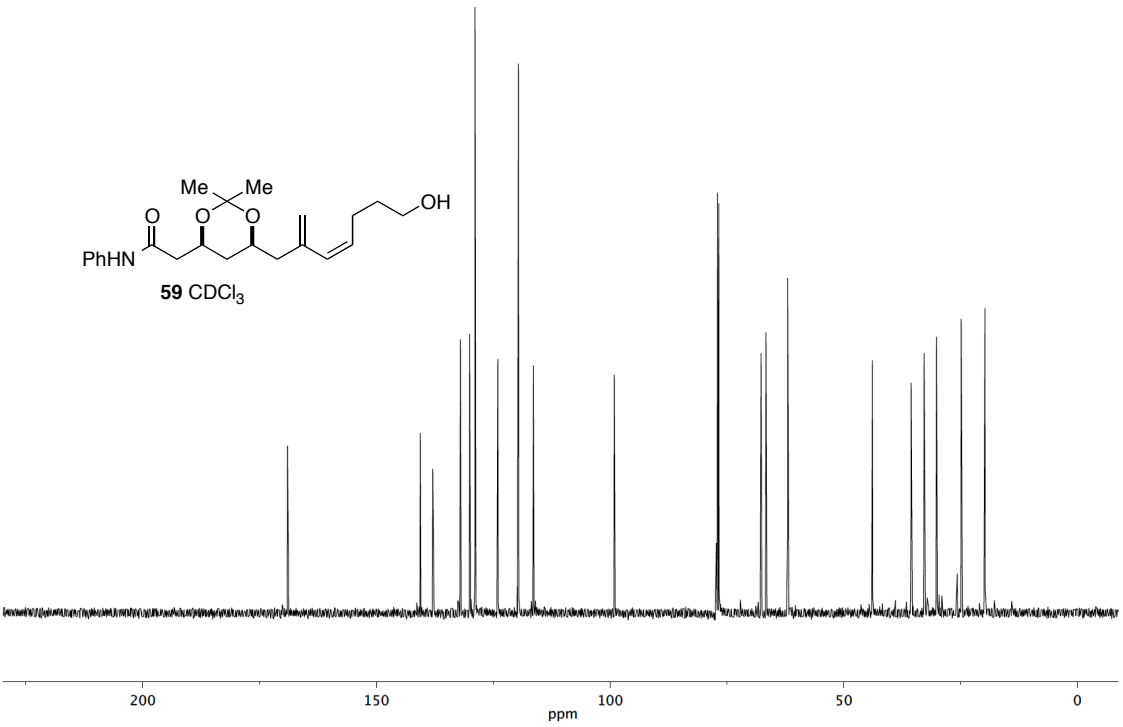

**27** $CDCl_3$



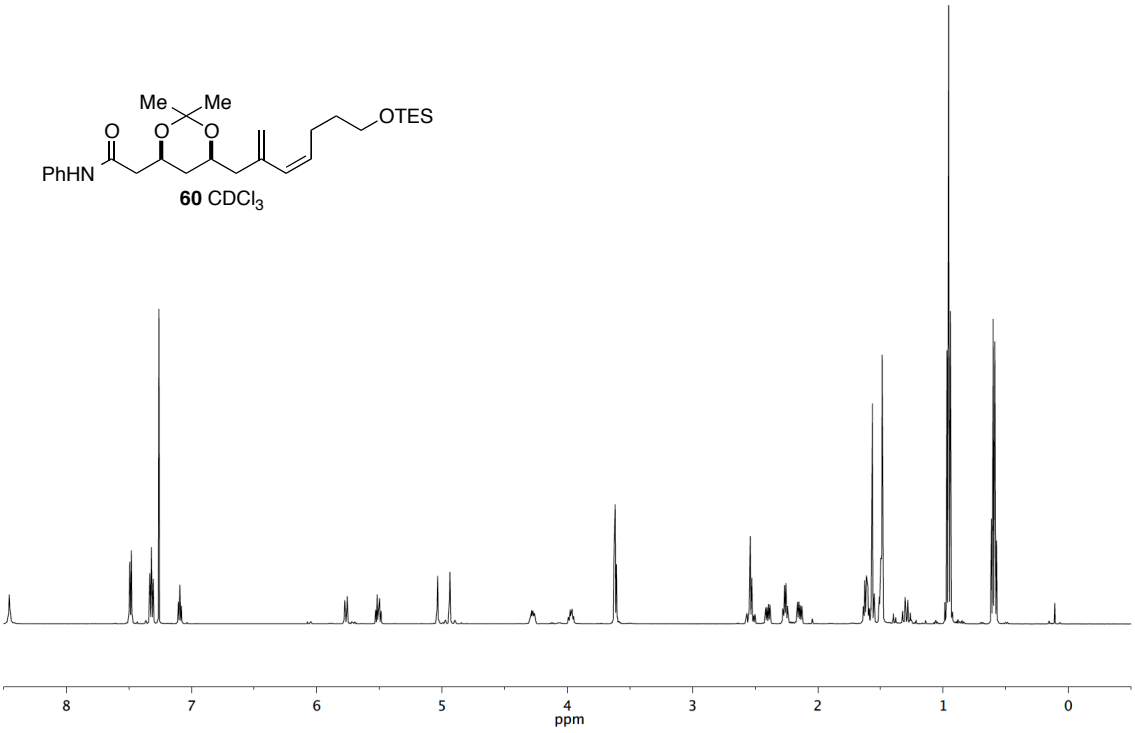

**27** $CDCl_3$

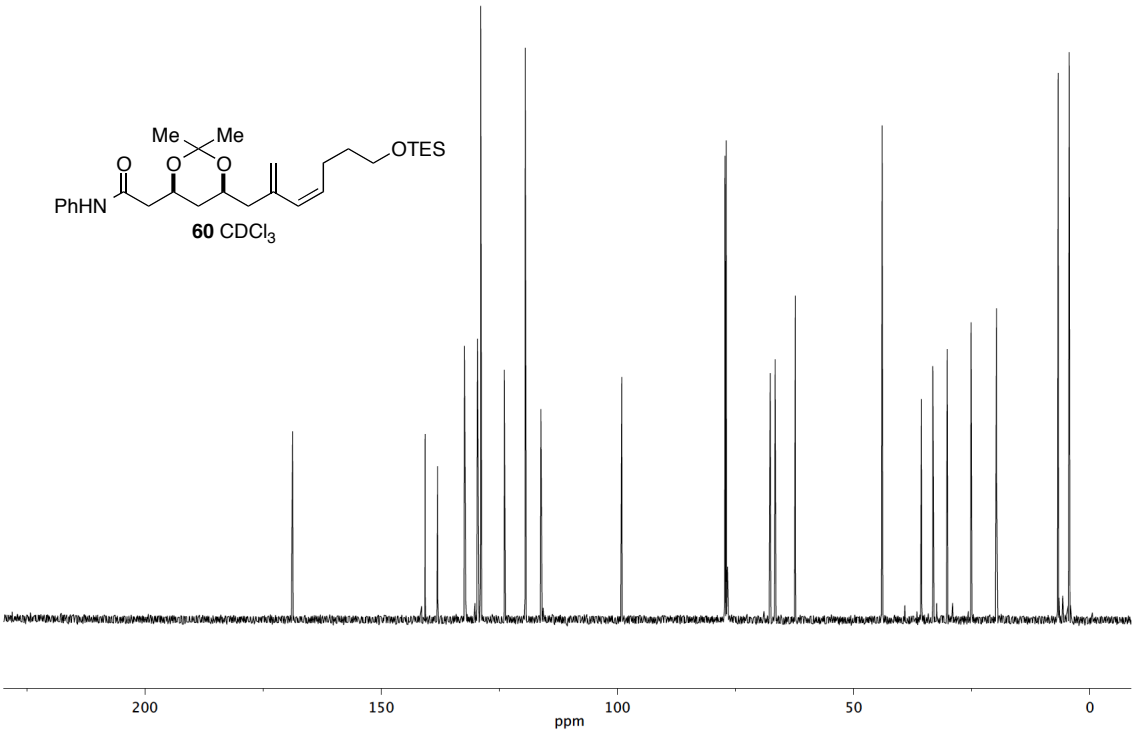


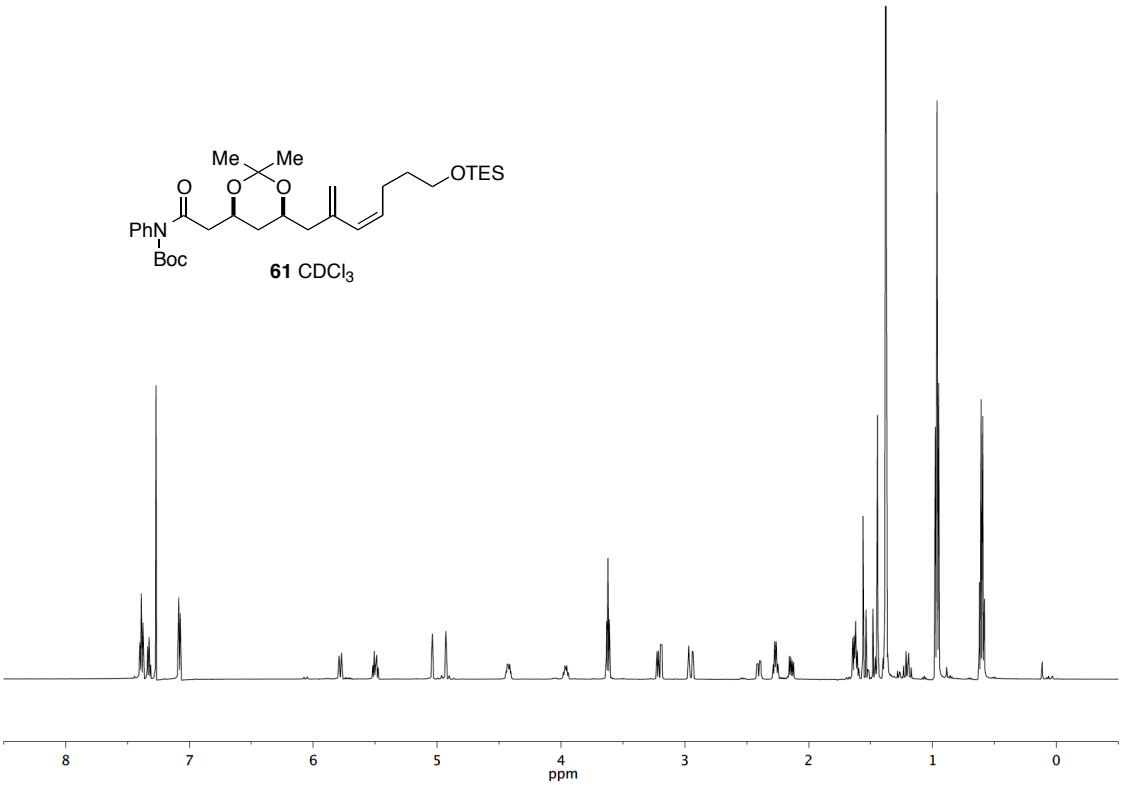

**59** $CDCl_3$



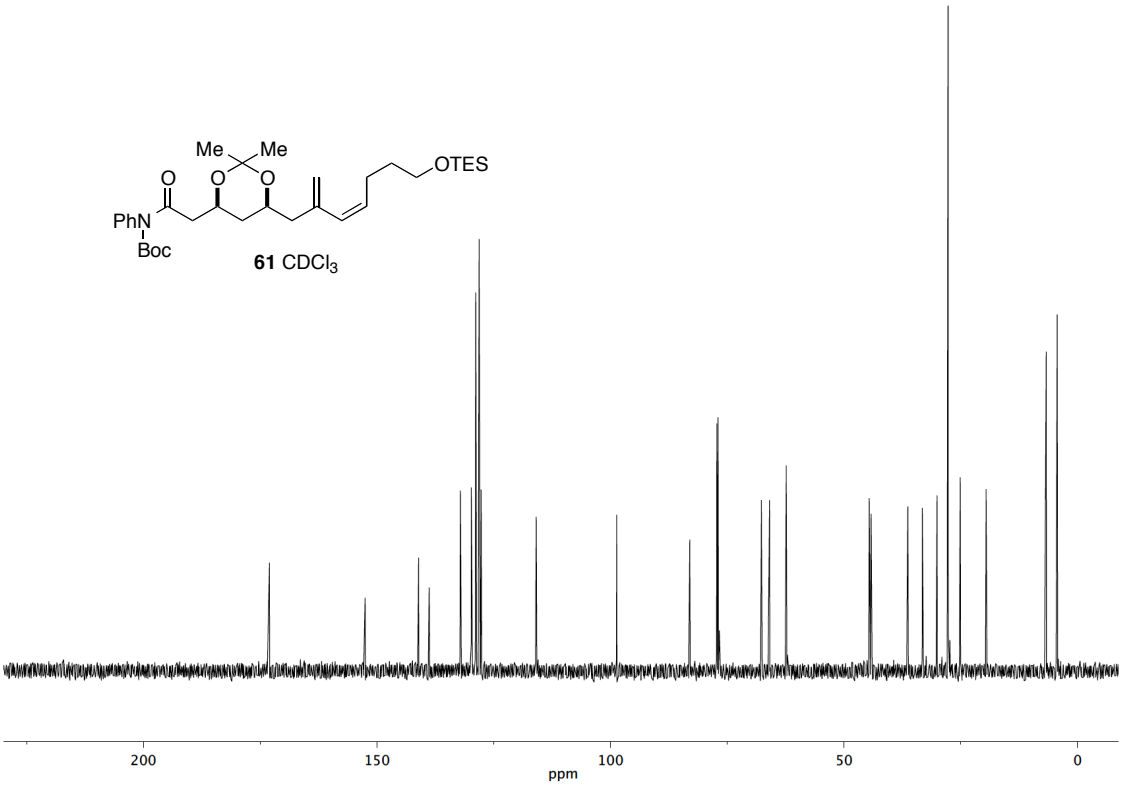

**59** $CDCl_3$


Me
Me
O
O
O
OTES
PhHN
60 CDCl3
8
7
6
5
4
3
2
1
0
ppm

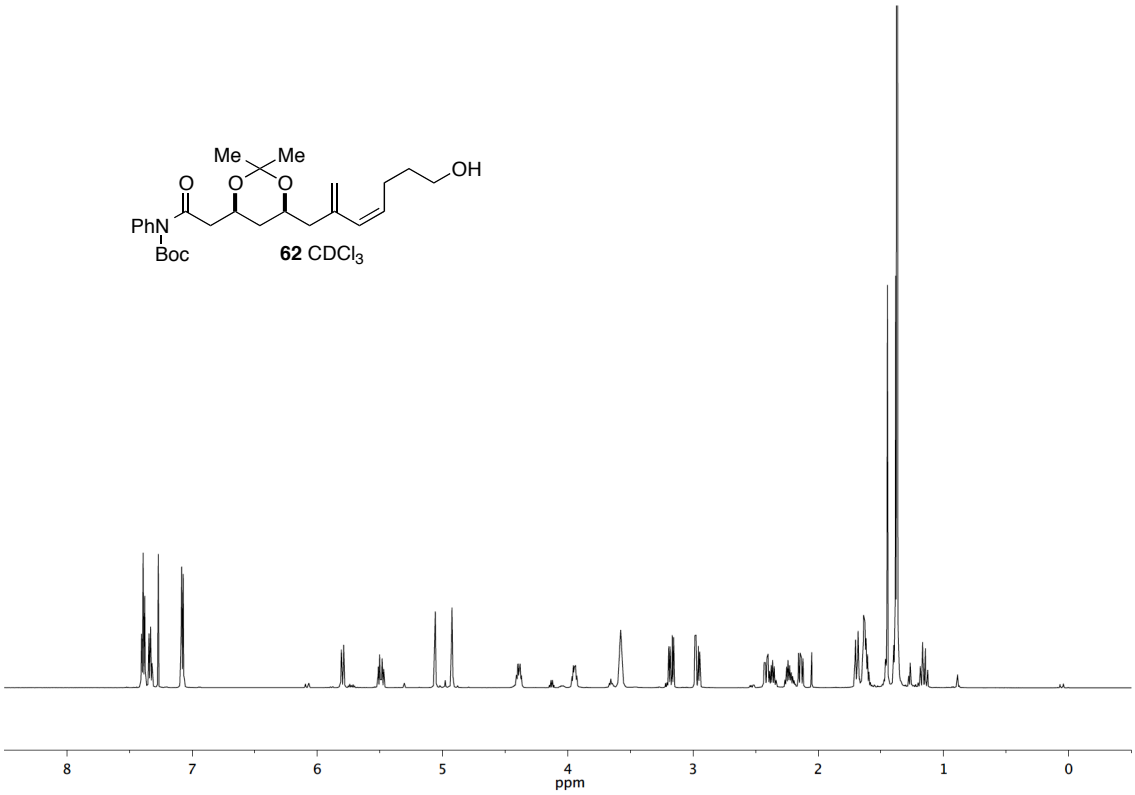

Me
Me
O
O
O
OTES
PhHN
60 CDCl3
200
150
100
50
0
ppm

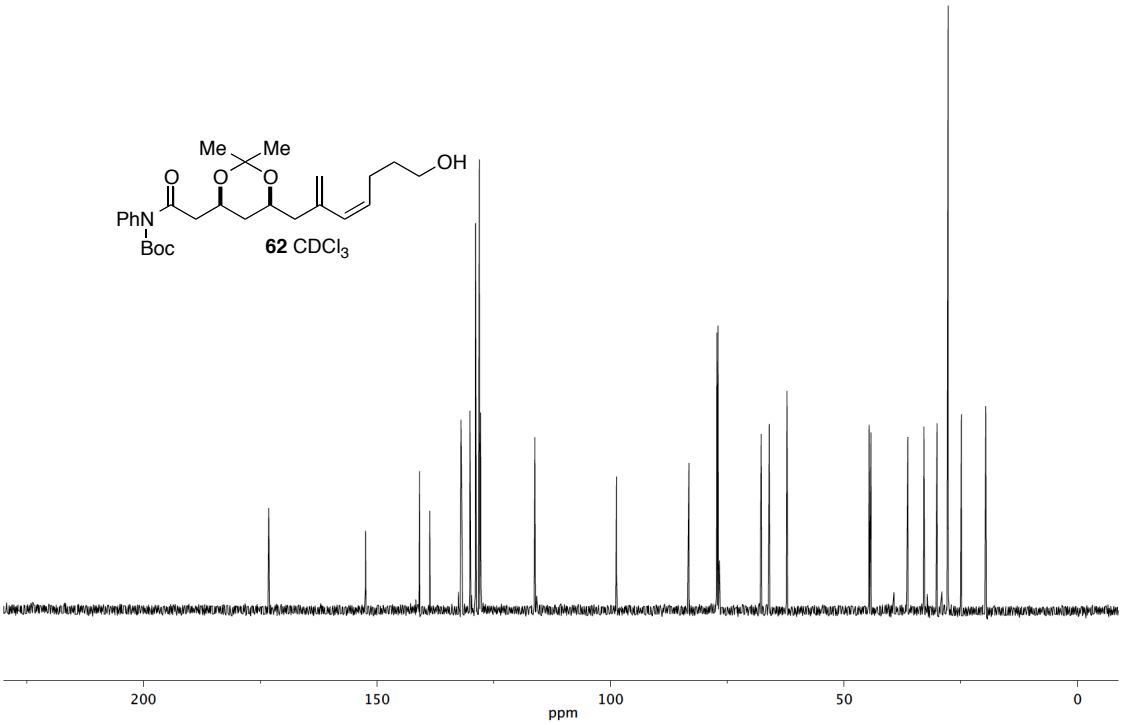


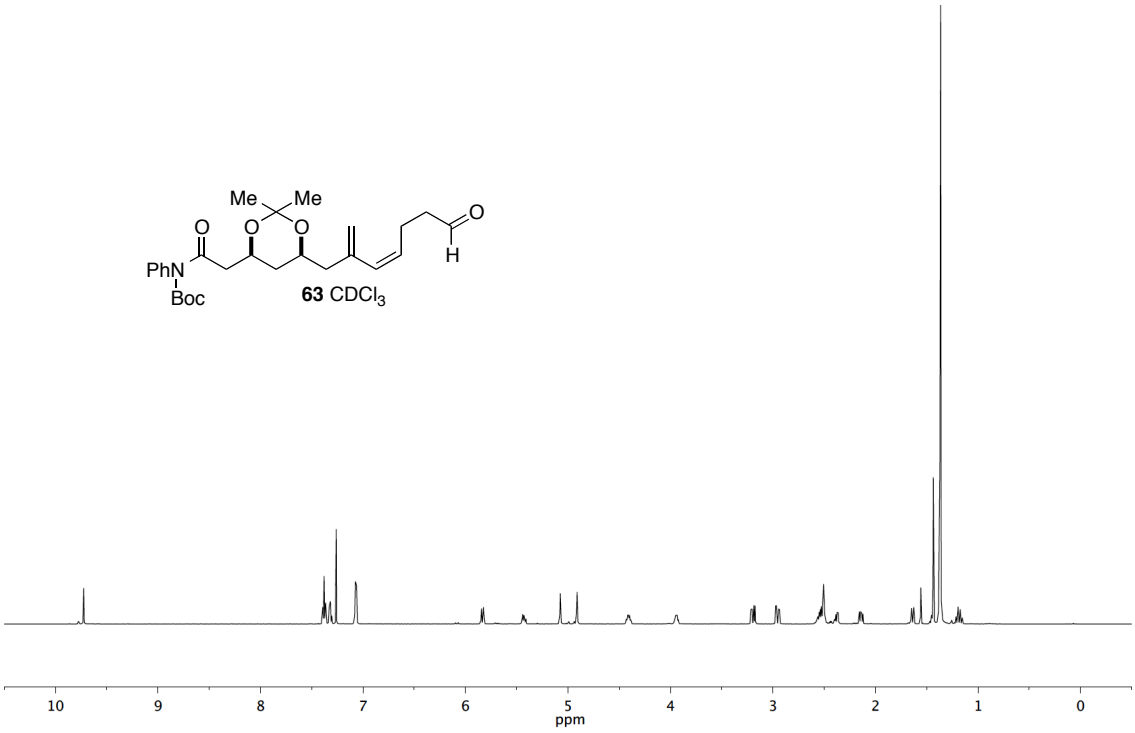

**61** $CDCl_3$

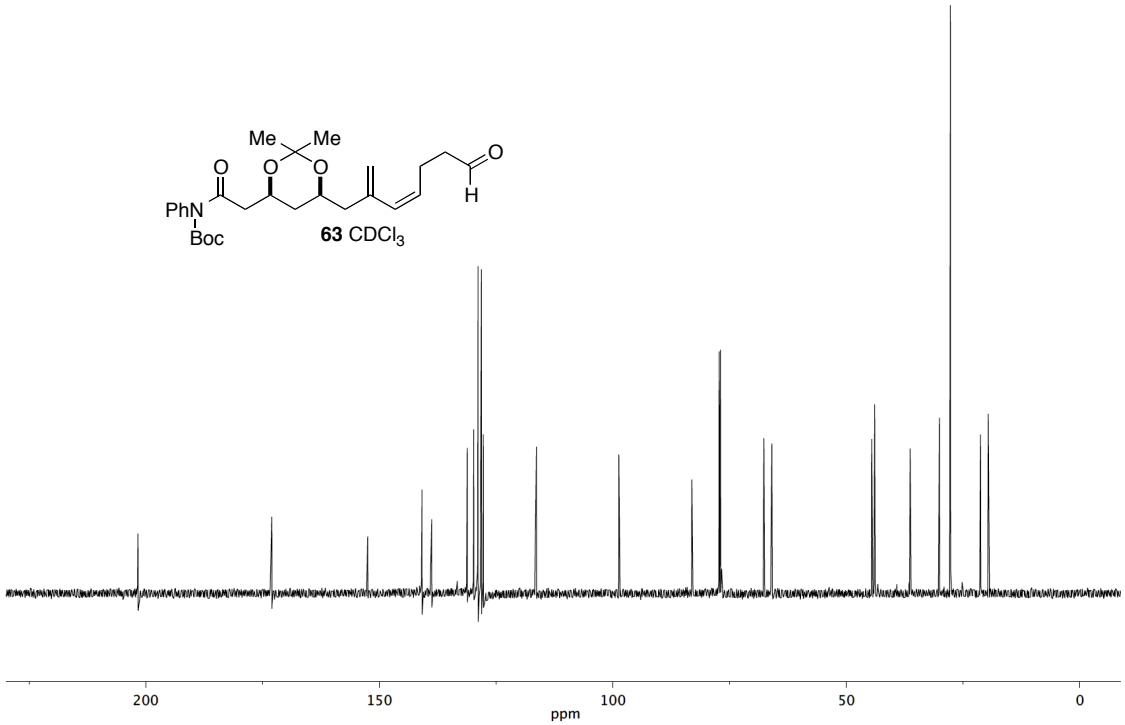


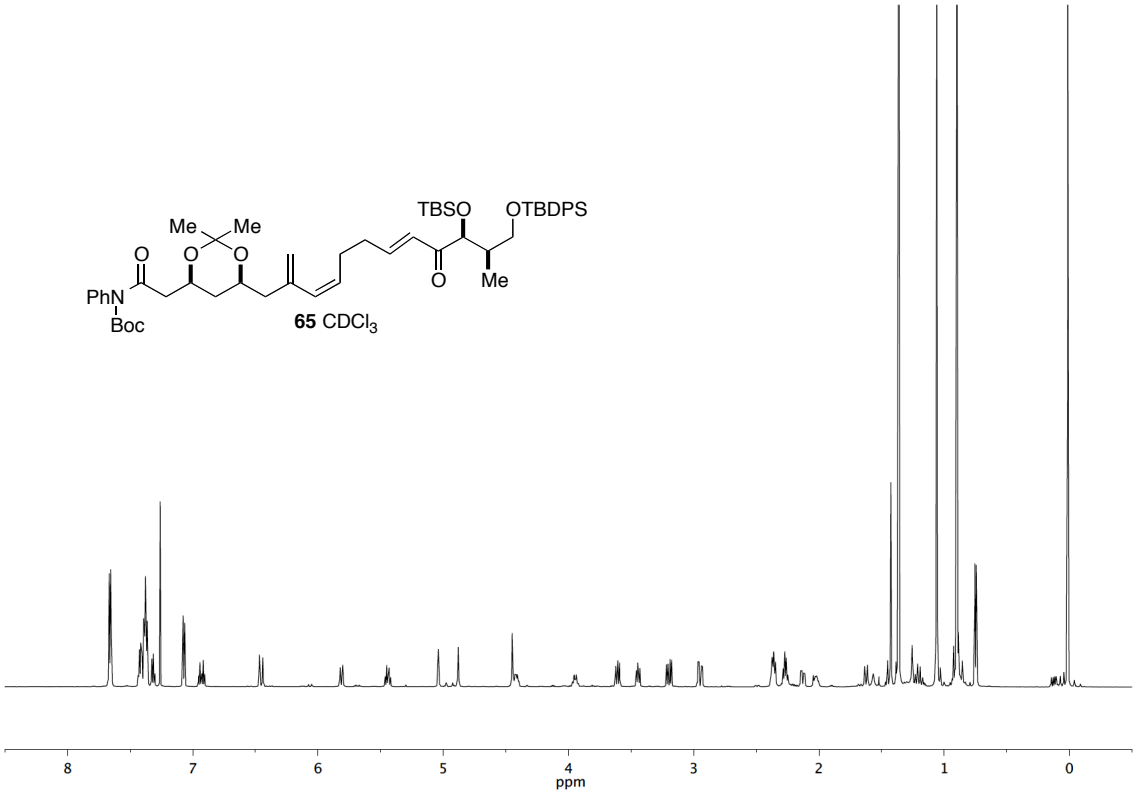

**61** $CDCl_3$

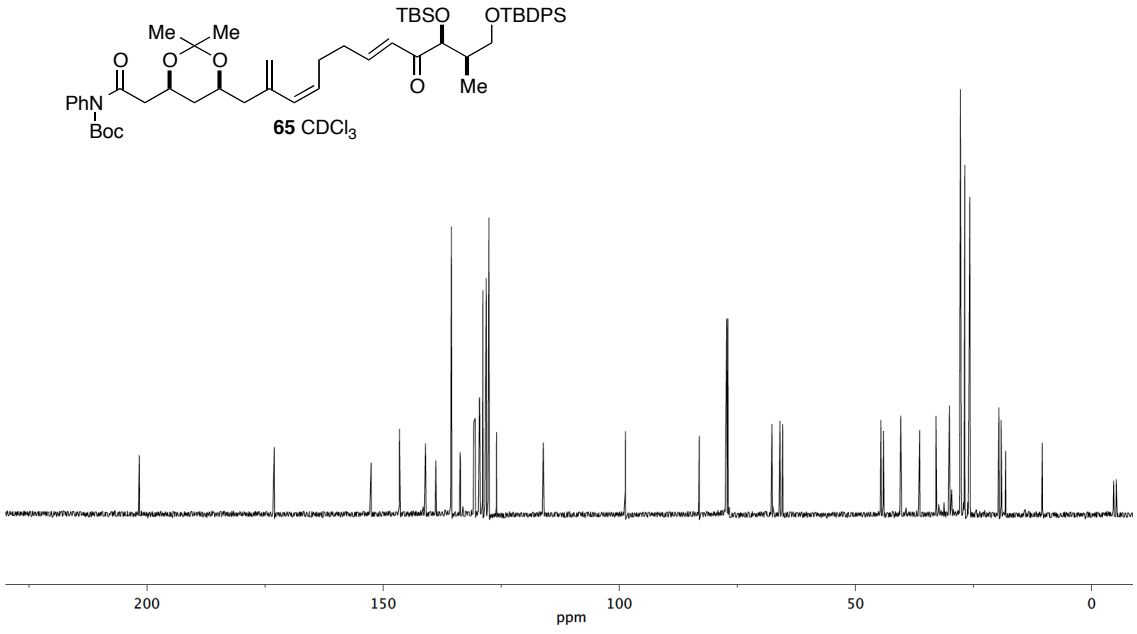

Me
Me
O
O
O
OH
PhN
Boc
62 CDCl3
8
7
6
5
4
3
2
1
0
ppm

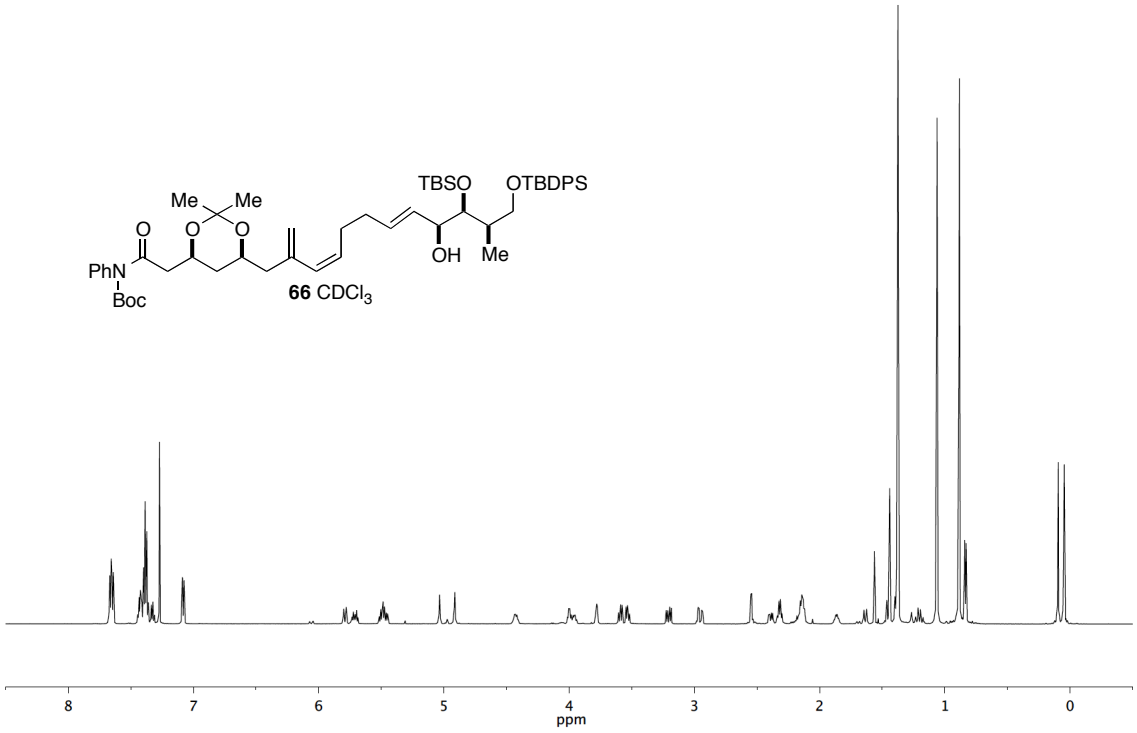

Me
Me
O
O
O
OH
PhN
Boc
62 CDCl3
200
150
100
50
0
ppm

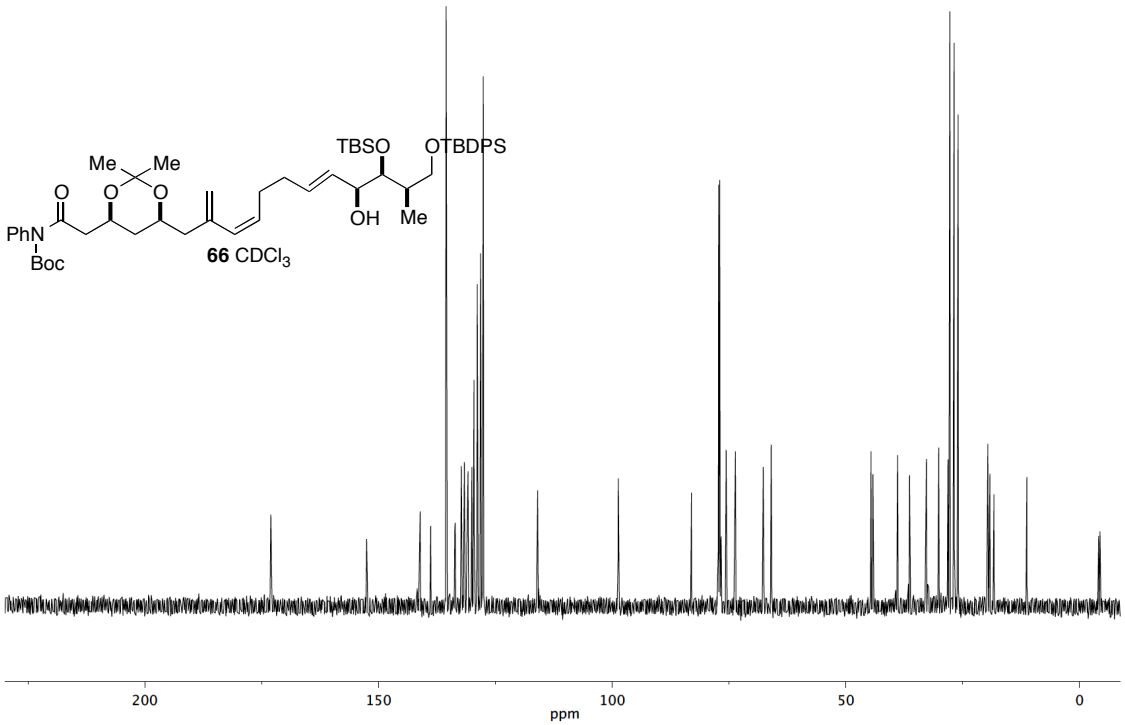

Me
Me
O
O
O
O
H
PhN
Boc
63 CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm

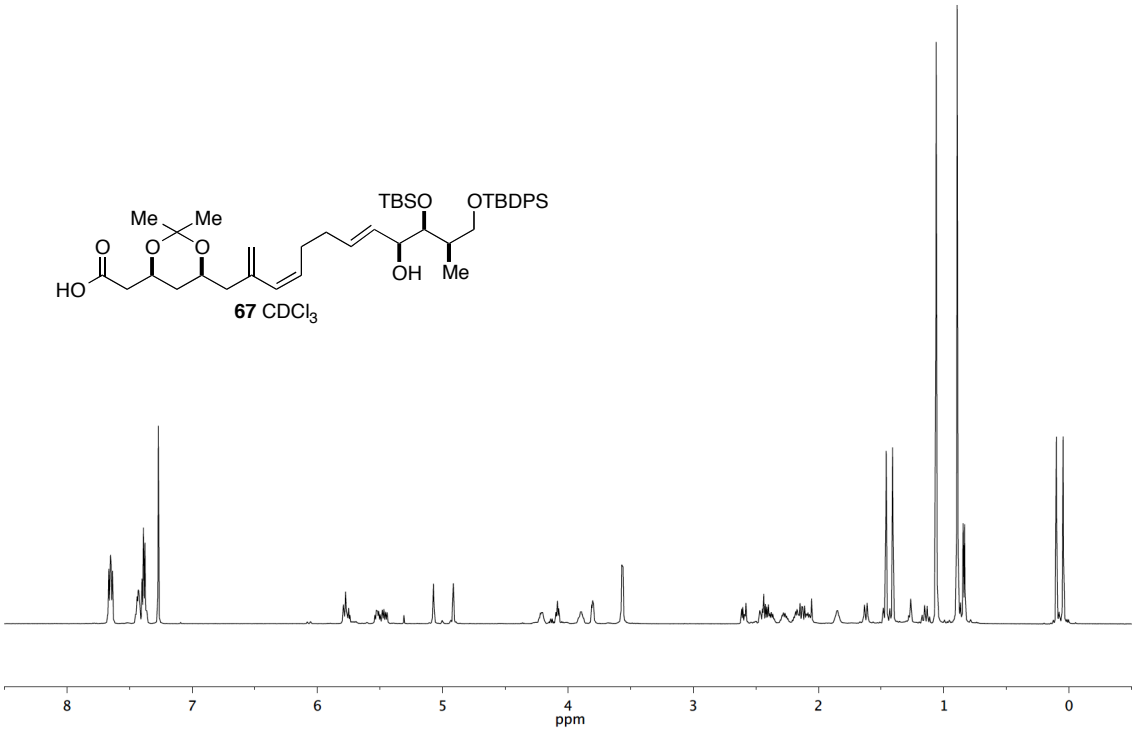

Me
Me
O
O
O
O
H
PhN
Boc
63 CDCl3
200
150
100
50
0
ppm


TBSO
OTBDPS
Me
Me
O
O
O
O
Me
PhN
Boc
65 CDCl3
8
7
6
5
4
3
2
1
0
ppm

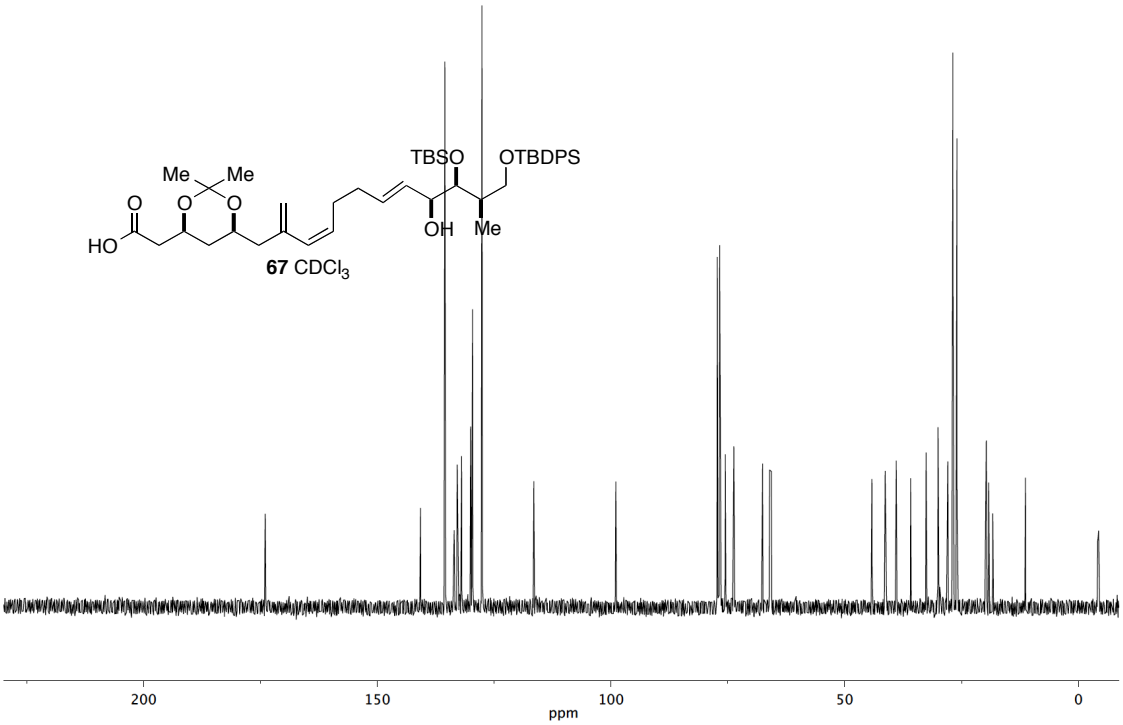

TBSO
OTBDPS
Me
Me
O
O
O
O
Me
PhN
Boc
65 CDCl3
200
150
100
50
0
ppm


TBSO
OTBDPS
Me
Me
O
O
O
OH
Me
PhN
Boc
66 CDCl3
8
7
6
5
4
3
2
1
0
ppm

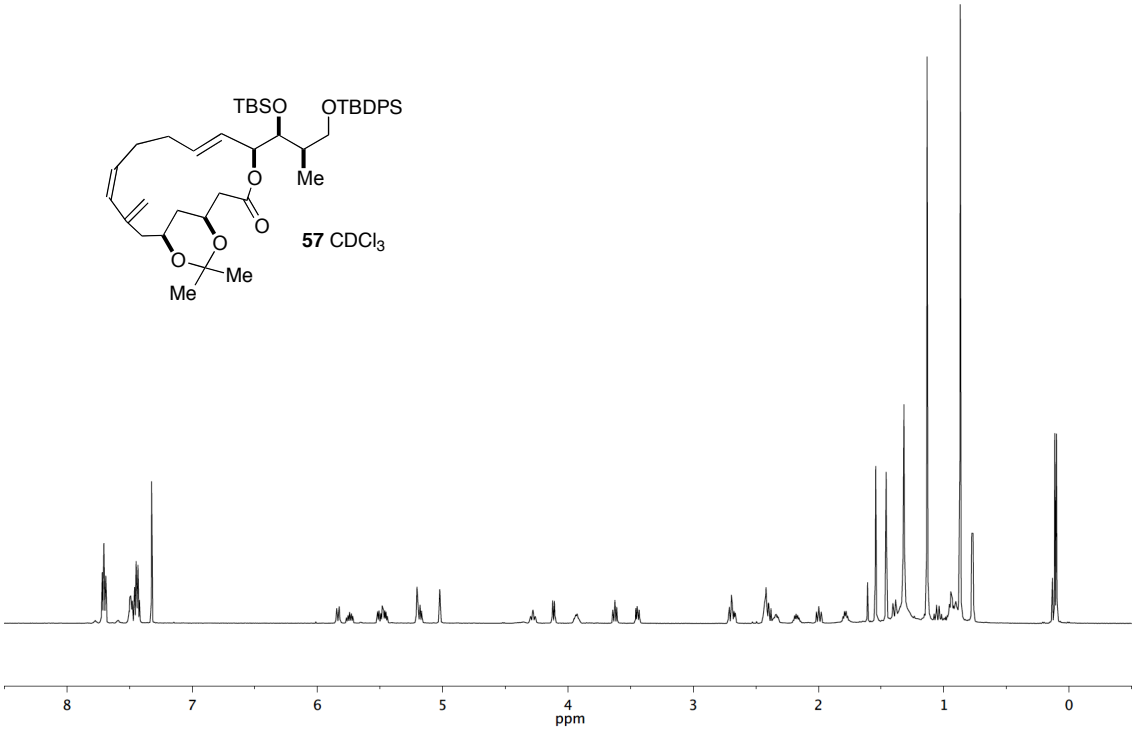

TBSO
OTBDPS
Me
Me
O
O
O
OH
Me
PhN
Boc
66 CDCl3
200
150
100
50
0
ppm

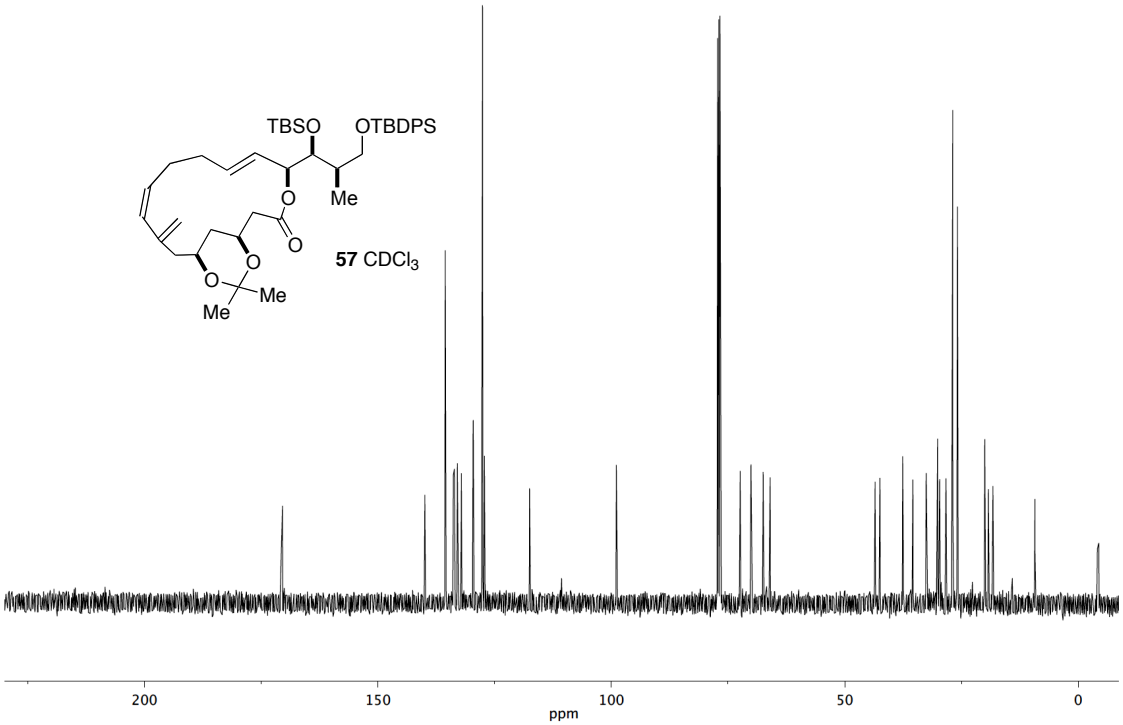


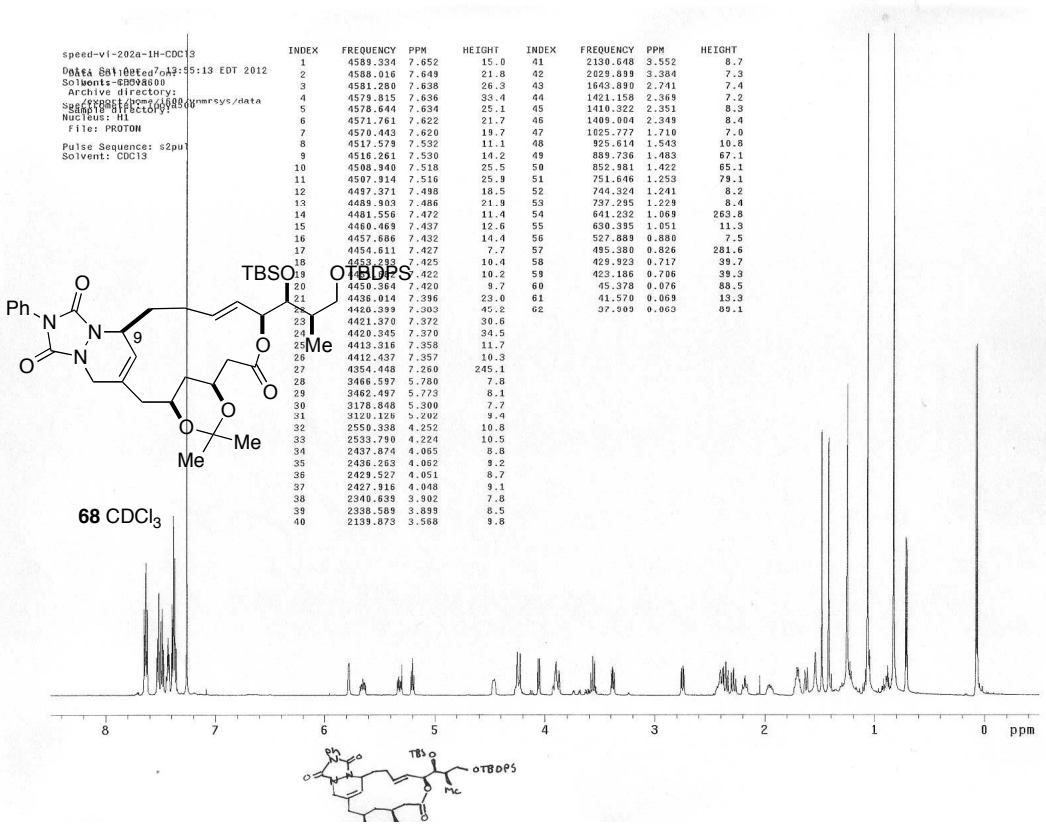

**67** $CDCl_3$



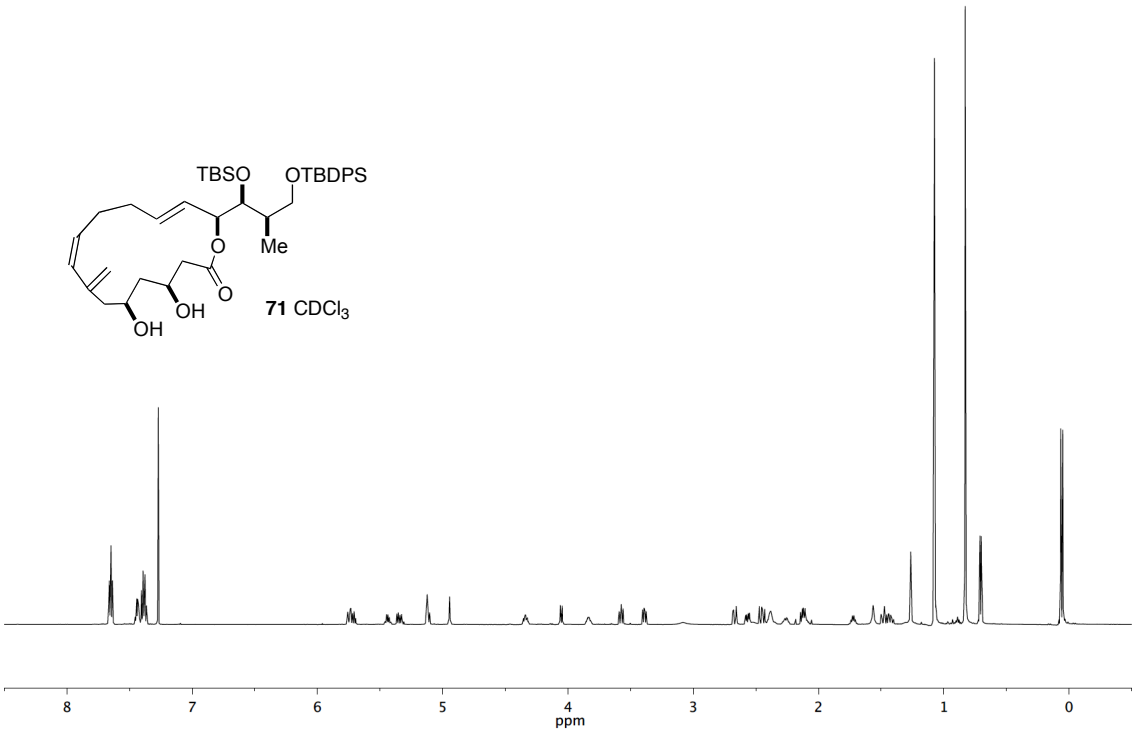

**67** $CDCl_3$

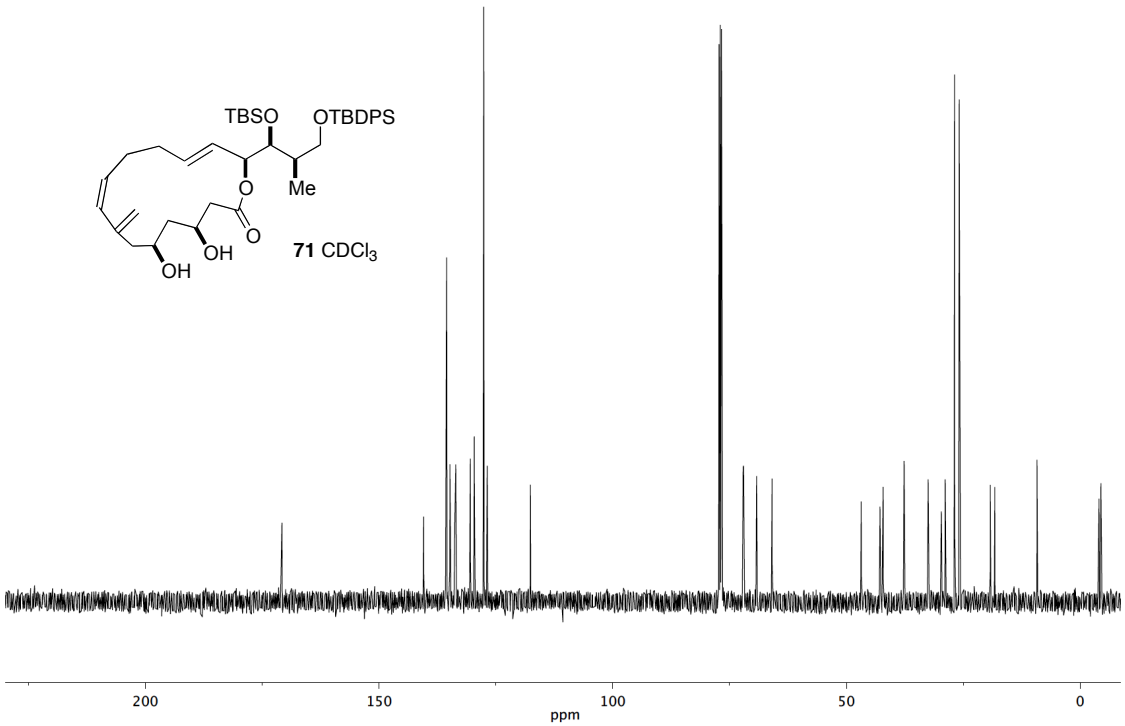

TBSO
OTBDPS
Me
O
O
O
O
Me
Me
57 CDCl3
8
7
6
5
4
3
2
1
0
ppm

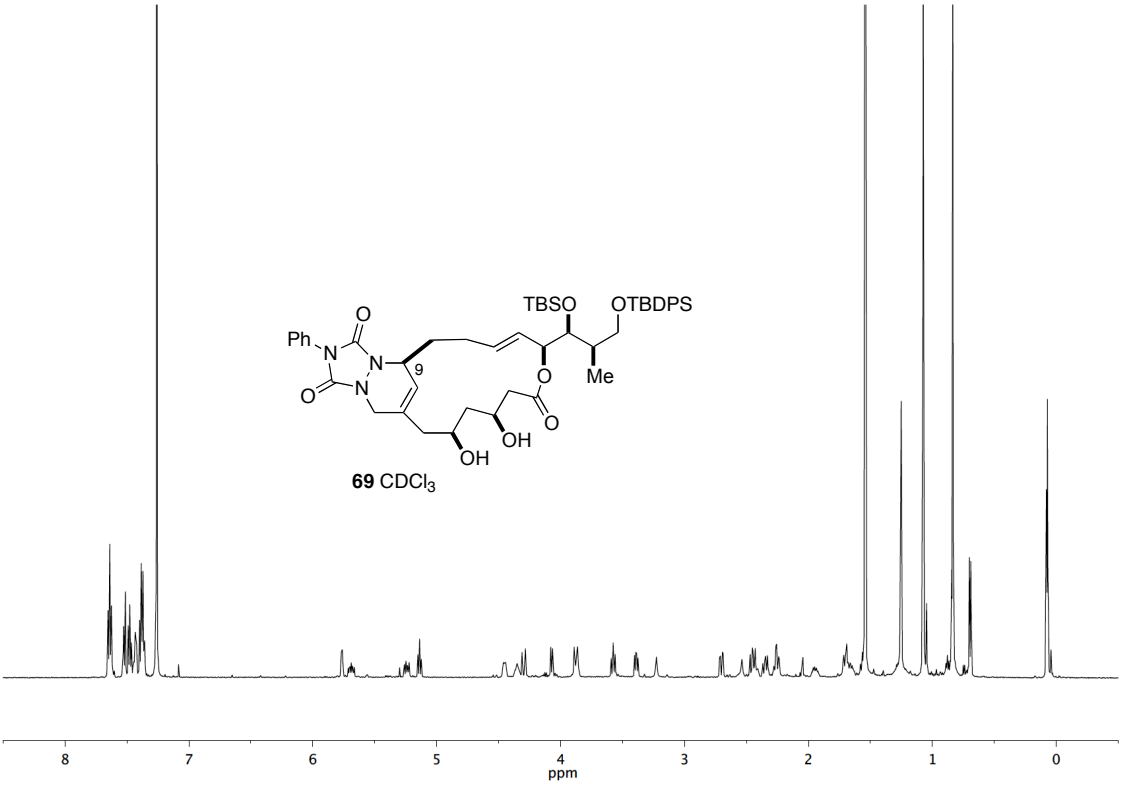

TBSO
OTBDPS
Me
O
O
O
O
Me
Me
57 CDCl3
200
150
100
50
0
ppm



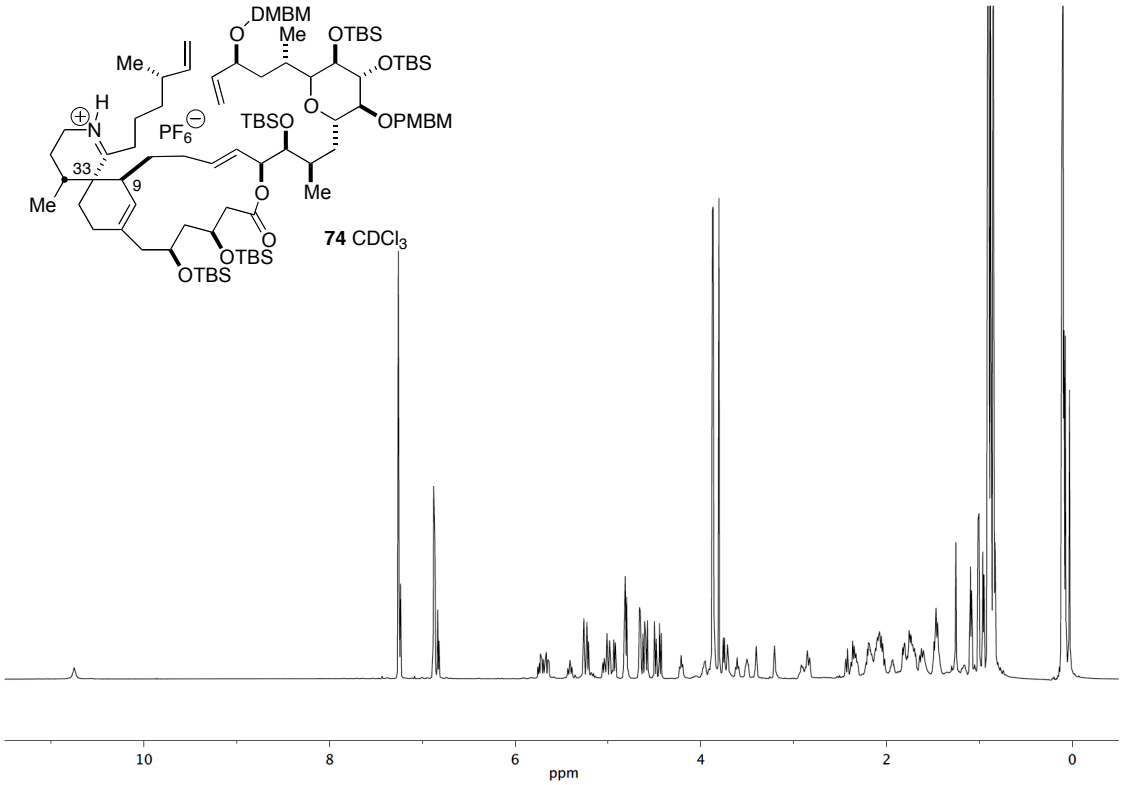

| INDEX | FREQUENCY | PPM | HEIGHT | INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|---|---|---|---|
| 1 | 4589.334 | 7.652 | 15.0 | 41 | 2130.648 | 3.552 | 8.7 |
| 2 | 4588.016 | 7.649 | 21.8 | 42 | 2029.899 | 3.384 | 7.3 |
| 3 | 4581.280 | 7.638 | 26.3 | 43 | 1643.890 | 2.741 | 7.4 |
| 4 | 4579.815 | 7.636 | 33.4 | 44 | 1421.158 | 2.369 | 7.2 |
| 5 | 4578.644 | 7.634 | 25.1 | 45 | 1410.322 | 2.351 | 8.3 |
| 6 | 4571.761 | 7.622 | 21.7 | 46 | 1409.004 | 2.349 | 8.4 |
| 7 | 4570.443 | 7.620 | 19.7 | 47 | 1025.777 | 1.710 | 7.0 |
| 8 | 4517.579 | 7.532 | 11.1 | 48 | 925.614 | 1.543 | 10.8 |
| 9 | 4516.261 | 7.530 | 14.2 | 49 | 889.736 | 1.483 | 67.1 |
| 10 | 4508.940 | 7.518 | 25.5 | 50 | 852.981 | 1.422 | 65.1 |
| 11 | 4507.914 | 7.516 | 25.9 | 51 | 751.646 | 1.253 | 79.1 |
| 12 | 4497.371 | 7.498 | 18.5 | 52 | 744.324 | 1.241 | 8.2 |
| 13 | 4489.903 | 7.486 | 21.9 | 53 | 737.295 | 1.229 | 8.4 |
| 14 | 4481.556 | 7.472 | 11.4 | 54 | 641.232 | 1.069 | 263.8 |
| 15 | 4480.469 | 7.437 | 12.6 | 55 | 630.395 | 1.051 | 11.3 |
| 16 | 4457.686 | 7.432 | 14.4 | 56 | 527.889 | 0.880 | 7.5 |
| 17 | 4454.611 | 7.427 | 7.7 | 57 | 495.380 | 0.826 | 281.6 |
| 18 | 4453.293 | 7.425 | 10.4 | 58 | 429.923 | 0.717 | 39.7 |
| 19 | 4452.147 | 7.422 | 10.2 | 59 | 423.186 | 0.706 | 39.3 |
| 20 | 4450.364 | 7.420 | 9.7 | 60 | 45.378 | 0.076 | 88.5 |
| 21 | 4436.014 | 7.396 | 23.0 | 61 | 41.570 | 0.069 | 13.3 |
| 22 | 4428.399 | 7.383 | 45.2 | 62 | 37.909 | 0.063 | 89.1 |
| 23 | 4421.370 | 7.372 | 30.6 | | | | |
| 24 | 4420.345 | 7.370 | 34.5 | | | | |
| 25 | 4413.316 | 7.358 | 11.7 | | | | |
| 26 | 4412.437 | 7.357 | 10.3 | | | | |
| 27 | 4354.448 | 7.260 | 245.1 | | | | |
| 28 | 3466.597 | 5.780 | 7.8 | | | | |
| 29 | 3462.497 | 5.773 | 8.1 | | | | |
| 30 | 3178.848 | 5.300 | 7.7 | | | | |
| 31 | 3129.126 | 5.202 | 9.4 | | | | |
| 32 | 2550.338 | 4.252 | 10.8 | | | | |
| 33 | 2533.790 | 4.224 | 10.5 | | | | |
| 34 | 2437.874 | 4.065 | 8.8 | | | | |
| 35 | 2436.263 | 4.062 | 9.2 | | | | |
| 36 | 2429.527 | 4.051 | 8.7 | | | | |
| 37 | 2427.916 | 4.048 | 9.1 | | | | |
| 38 | 2340.639 | 3.902 | 7.8 | | | | |
| 39 | 2338.589 | 3.899 | 8.5 | | | | |
| 40 | 2139.873 | 3.568 | 9.8 | | | | |


TBSO
OTBDPS
Me
O
O
OH
OH
71 CDCl3
8
7
6
5
4
3
2
1
0
ppm

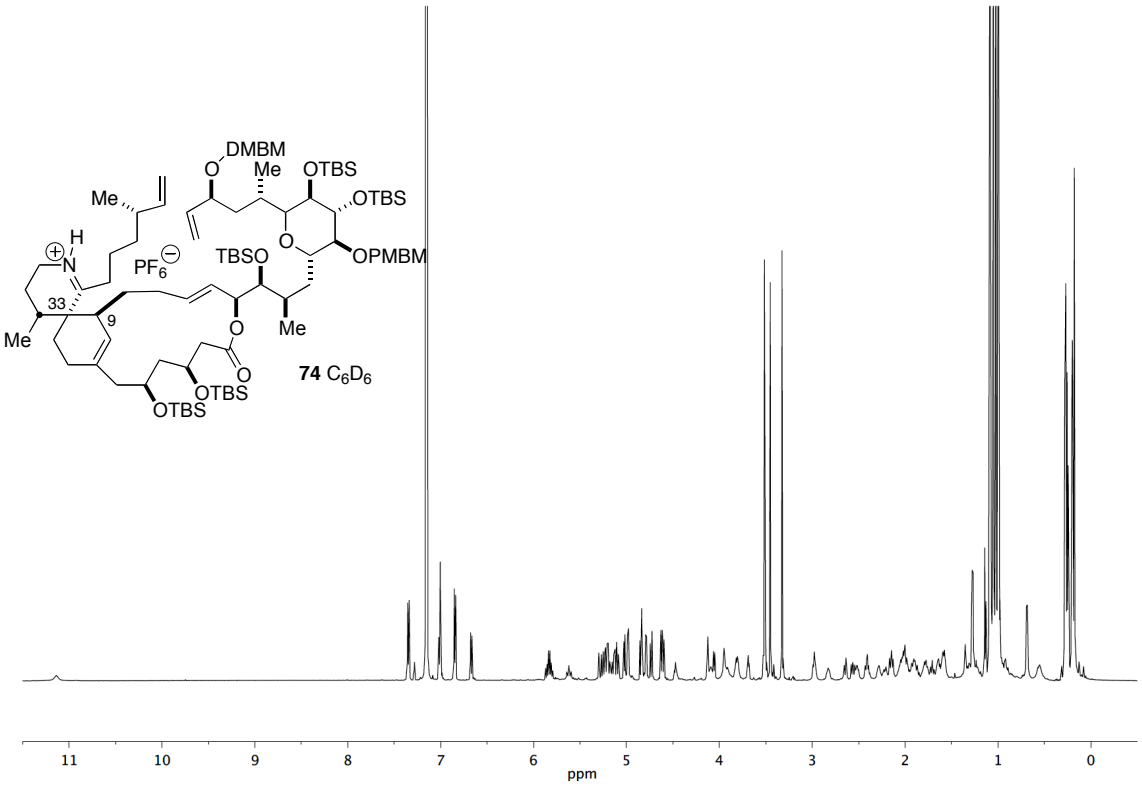

TBSO
OTBDPS
Me
O
O
OH
OH
71 CDCl3
200
150
100
50
0
ppm

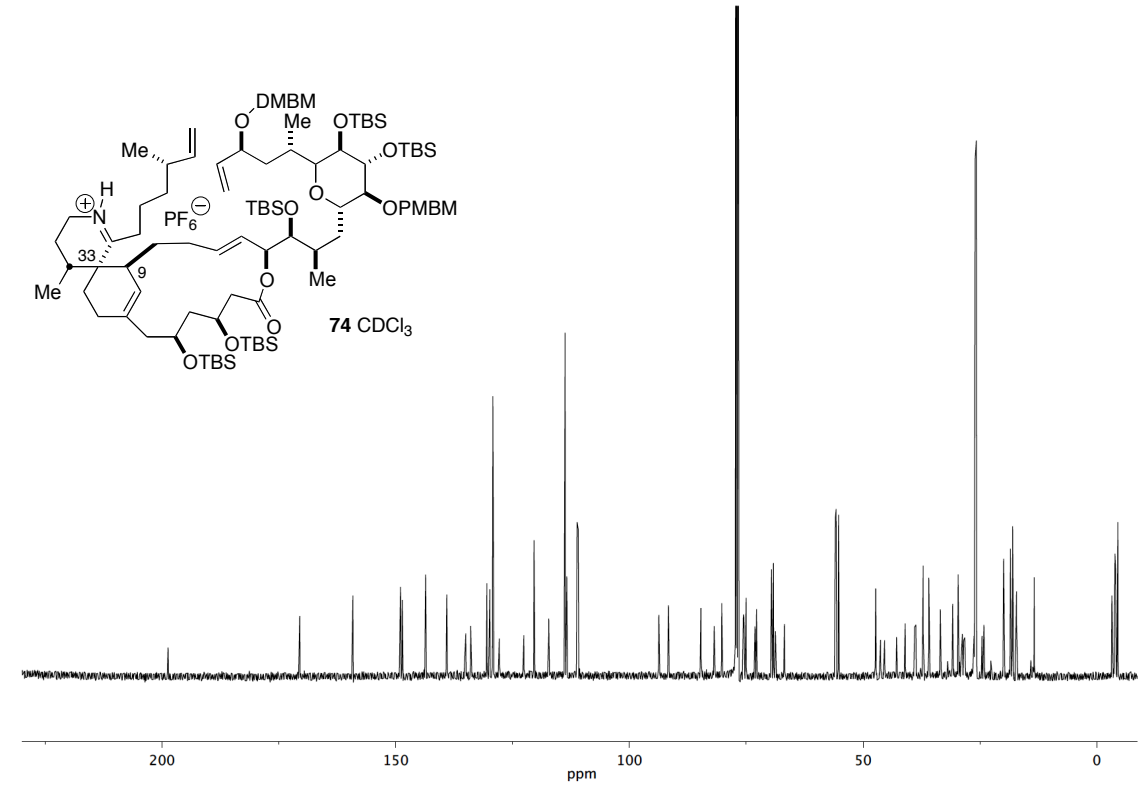


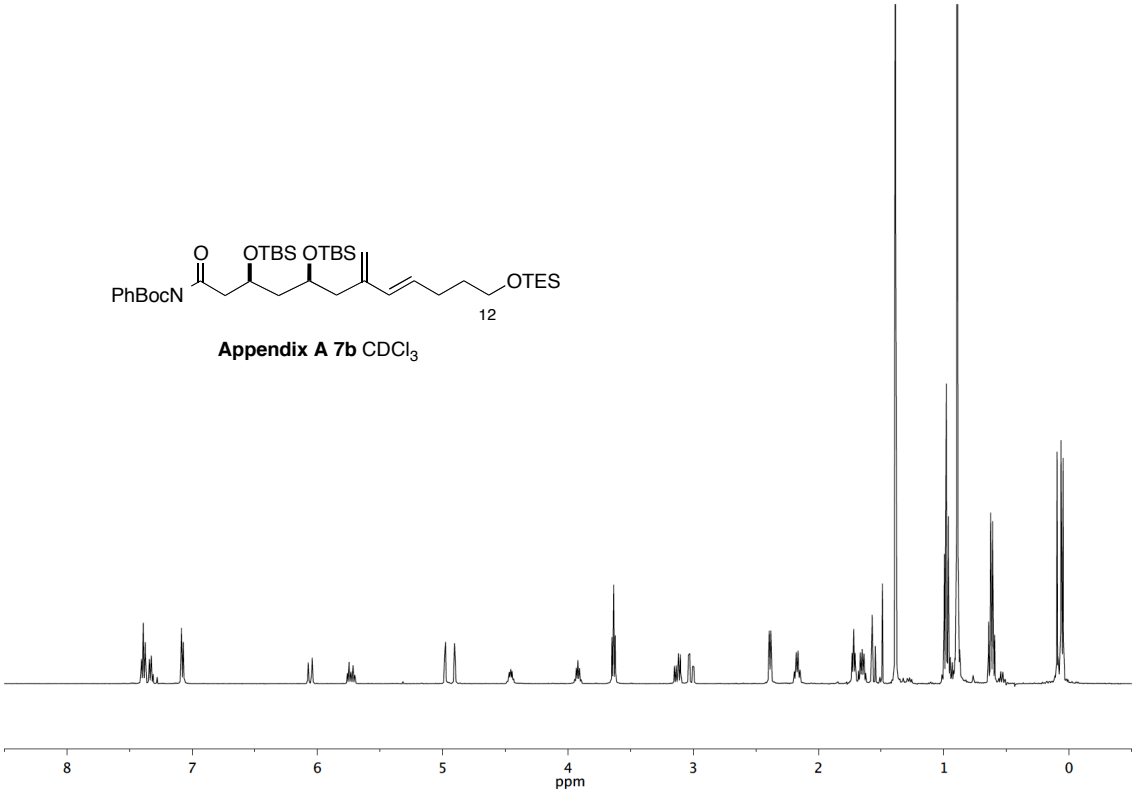

**69** $CDCl_3$



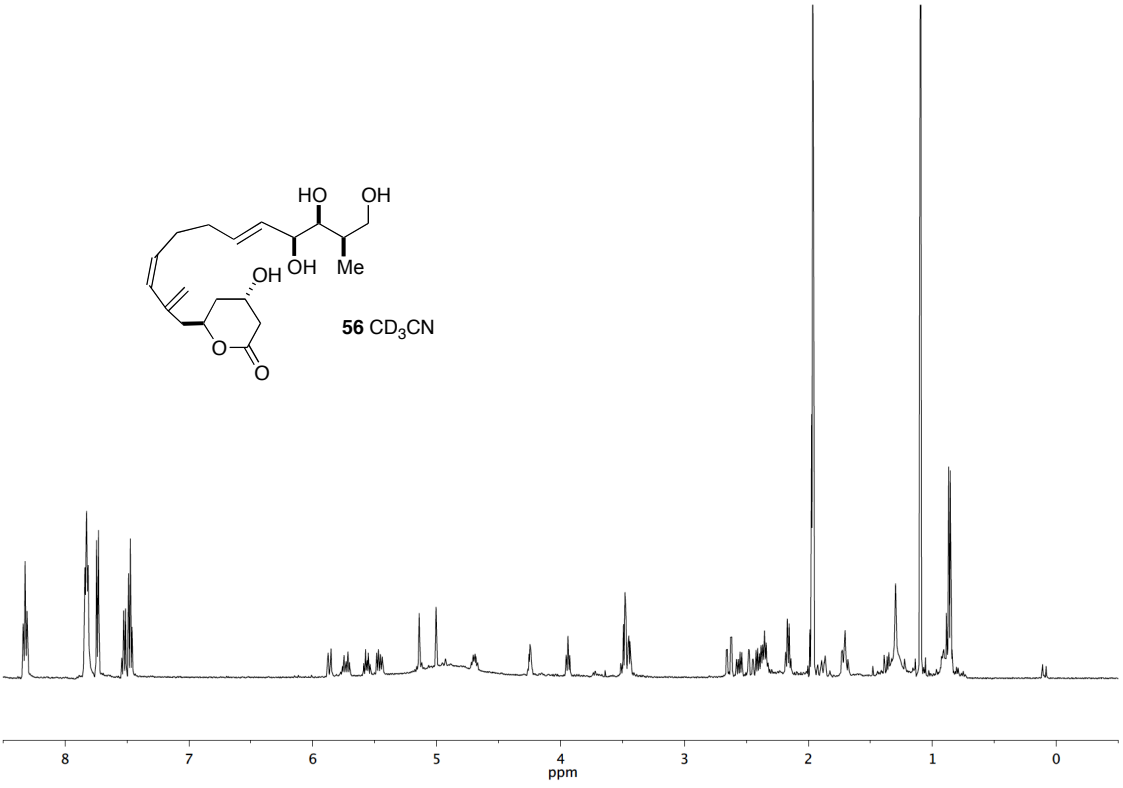

**74** $CDCl_3$


DMBM
Me
OTBS
OTBS
Me
H
N
PF6
TBSO
OPMBM
33
9
Me
O
Me
O
OTBS
OTBS
74 C6D6
11
10
9
8
7
6
5
4
3
2
1
0
ppm

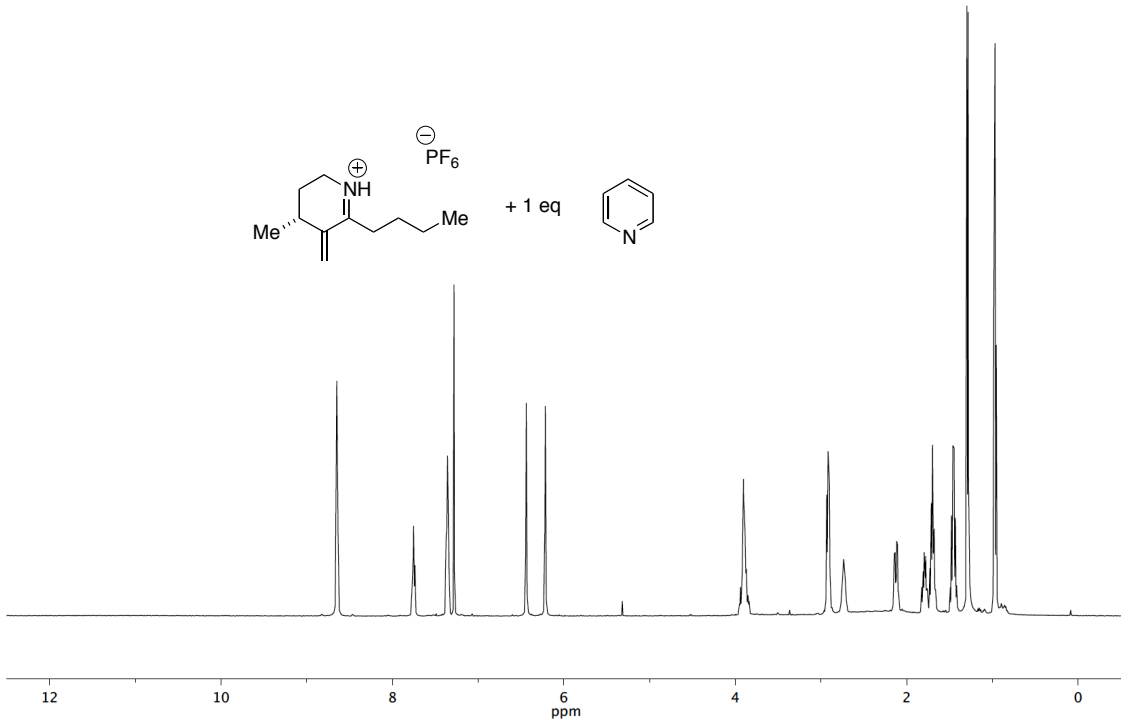

DMBM
Me
OTBS
OTBS
Me
H
N
PF6
TBSO
OPMBM
33
9
Me
O
Me
O
OTBS
OTBS
74 CDCl3
200
150
100
50
0
ppm

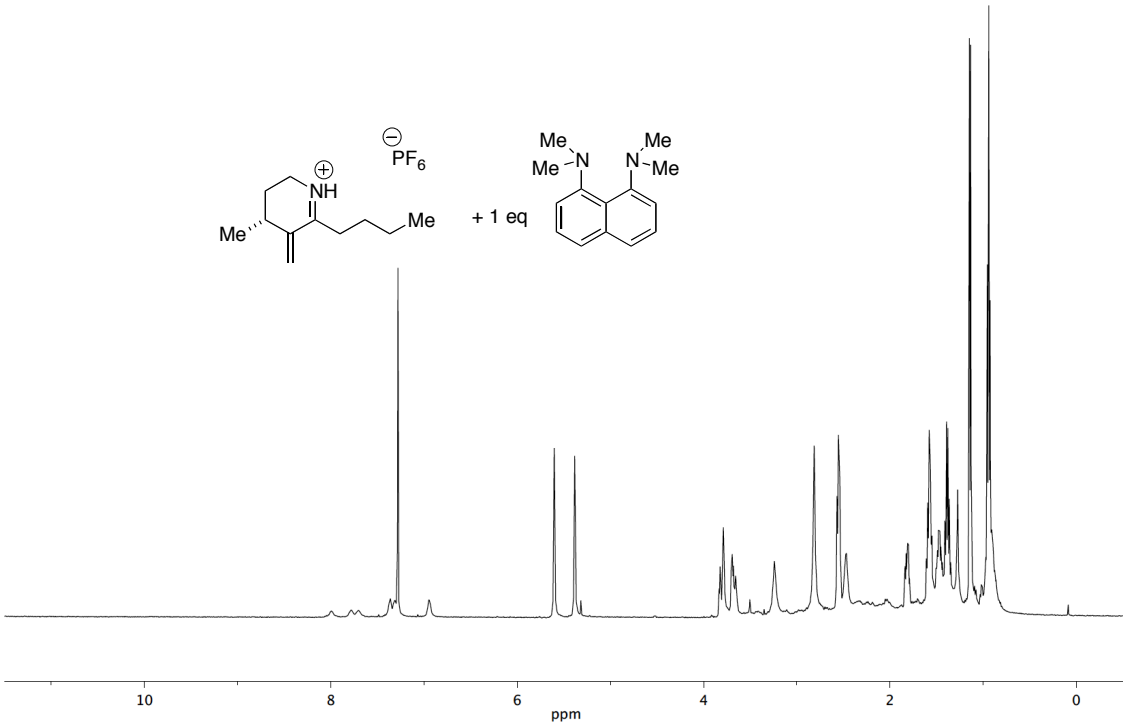



**Appendix A 7b** $CDCl_3$

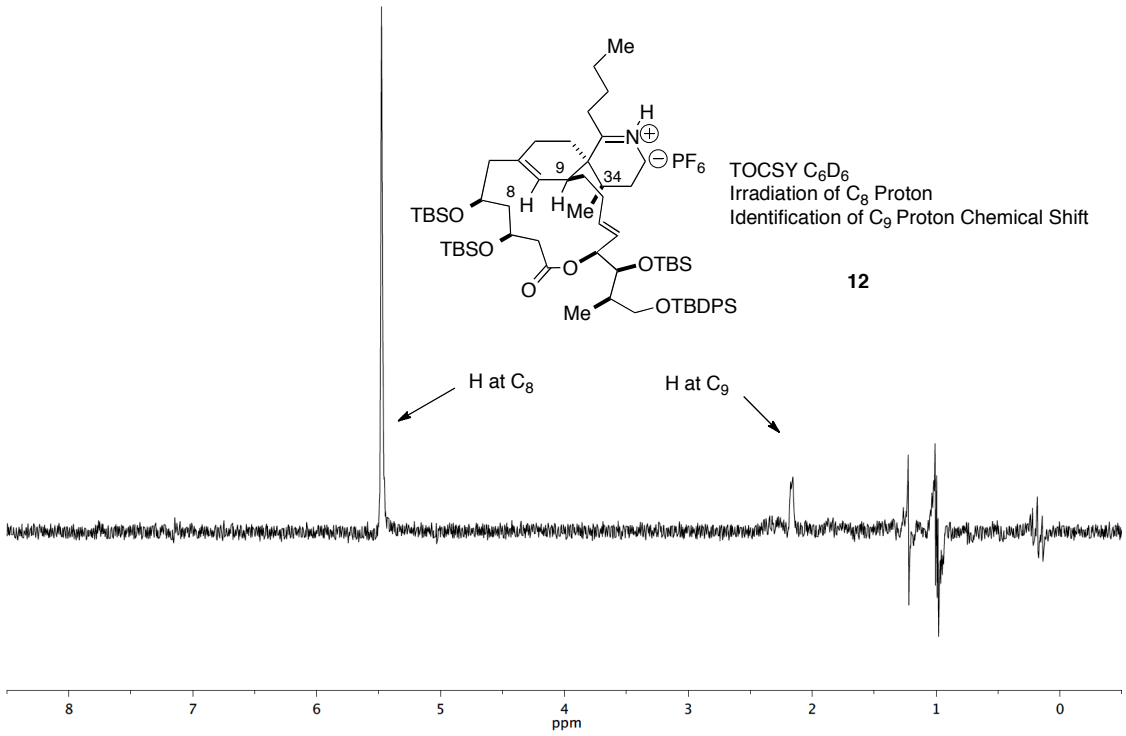


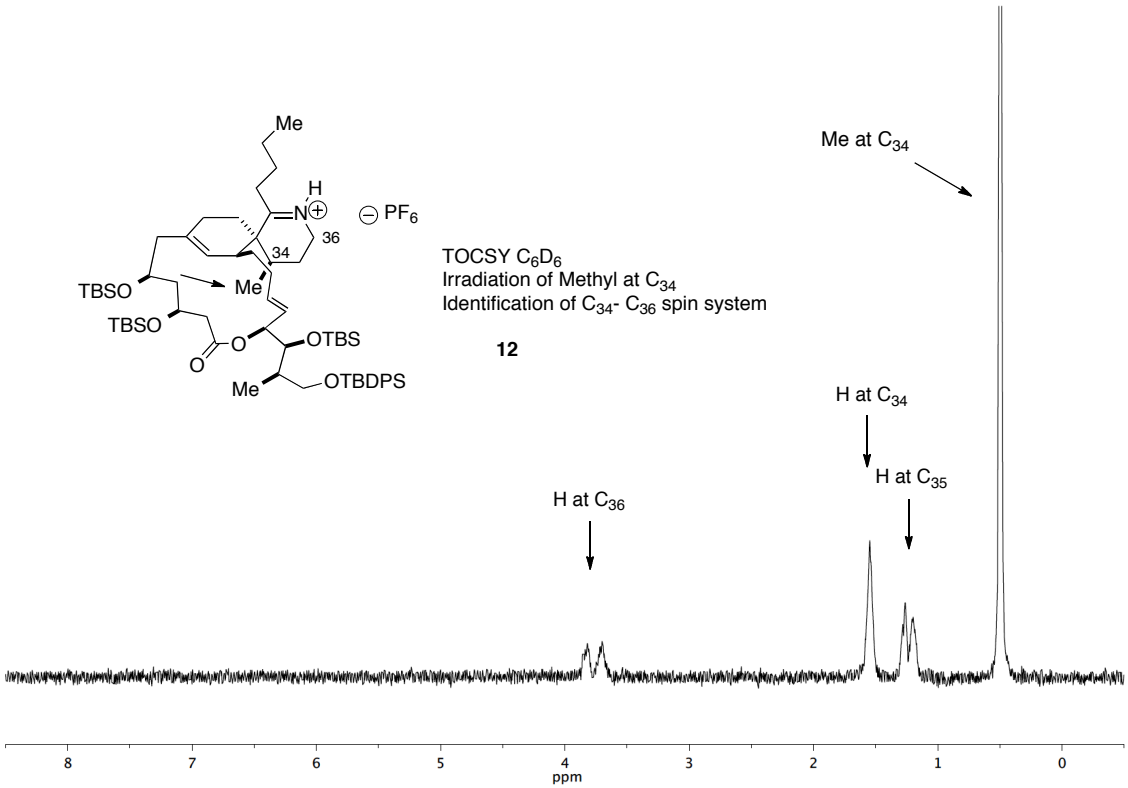

**56** $CD_3CN$

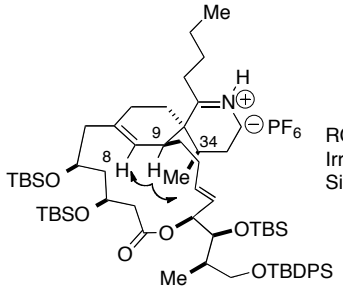

PF6
NH
Me
Me
+ 1 eq
N
12
10
8
6
4
2
0
ppm


PF6
NH
Me
Me
+ 1 eq
Me
Me
N
N
Me
Me
10
8
6
4
2
0
ppm

# V. Spectra of Hydrogenation Bicycle and Diels—Alder Adducts

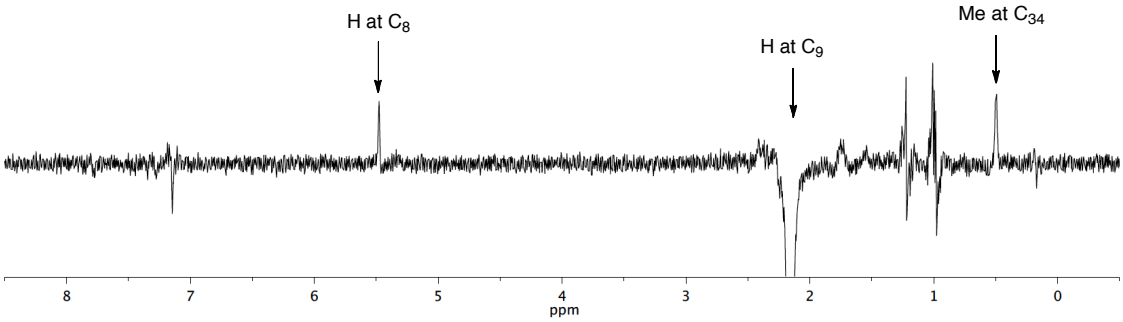


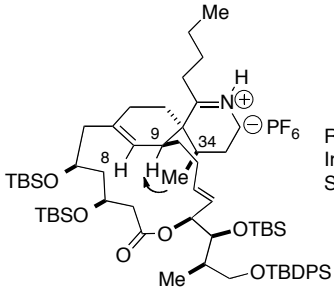






ROESY $C_6D_6$
Irradiation of $C_9$ Proton
Signals at $C_8$ Proton and $C_{34}$ Methyl

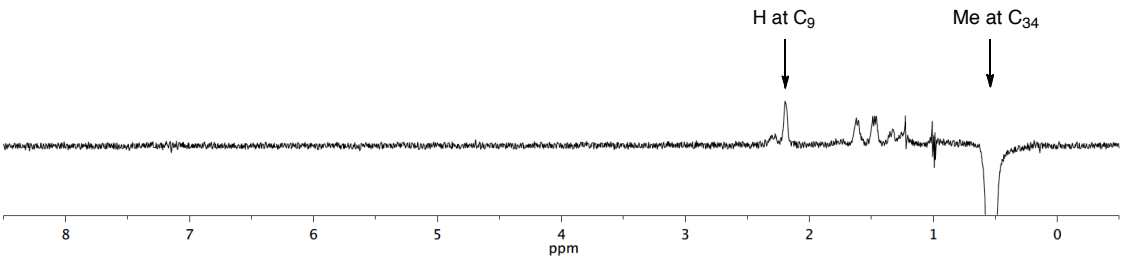
**12**

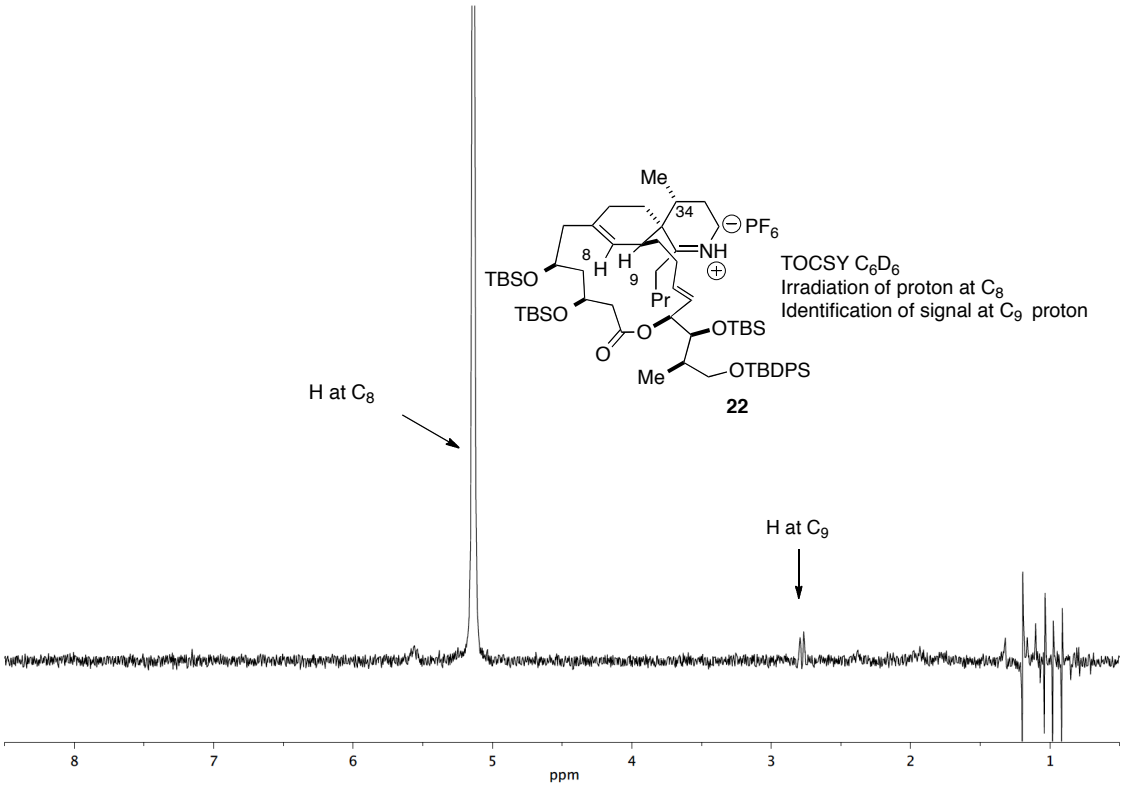


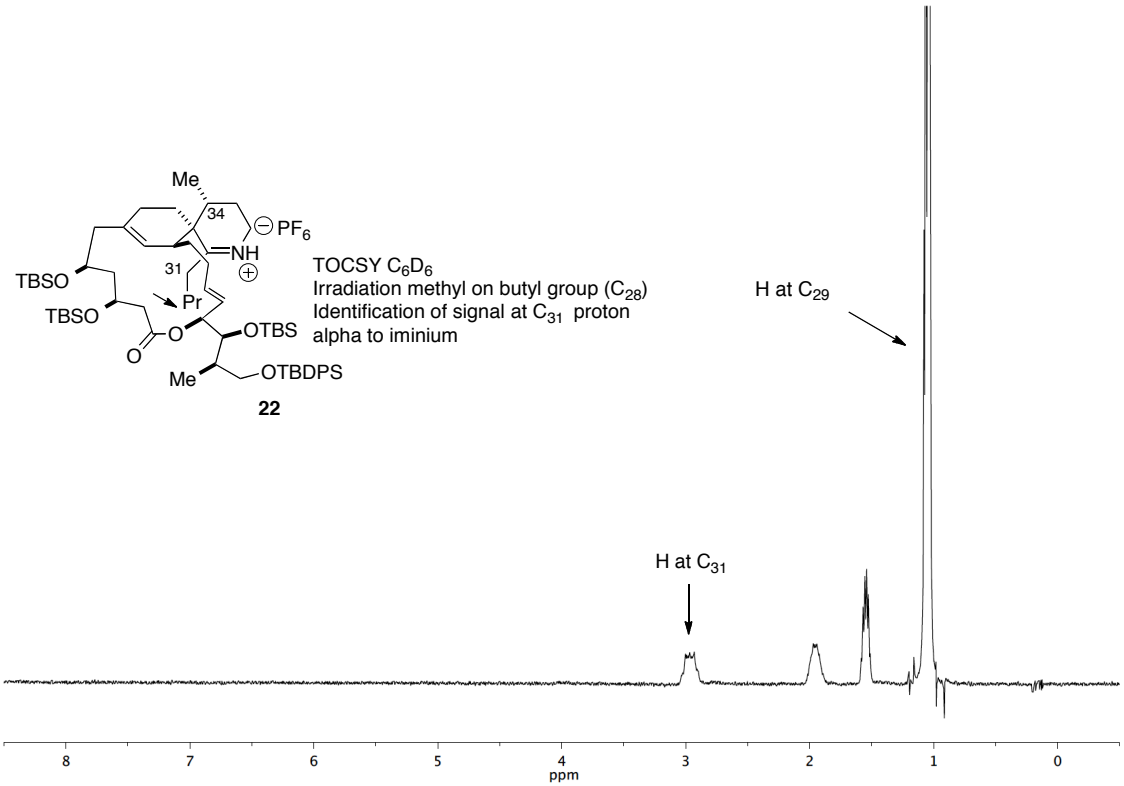



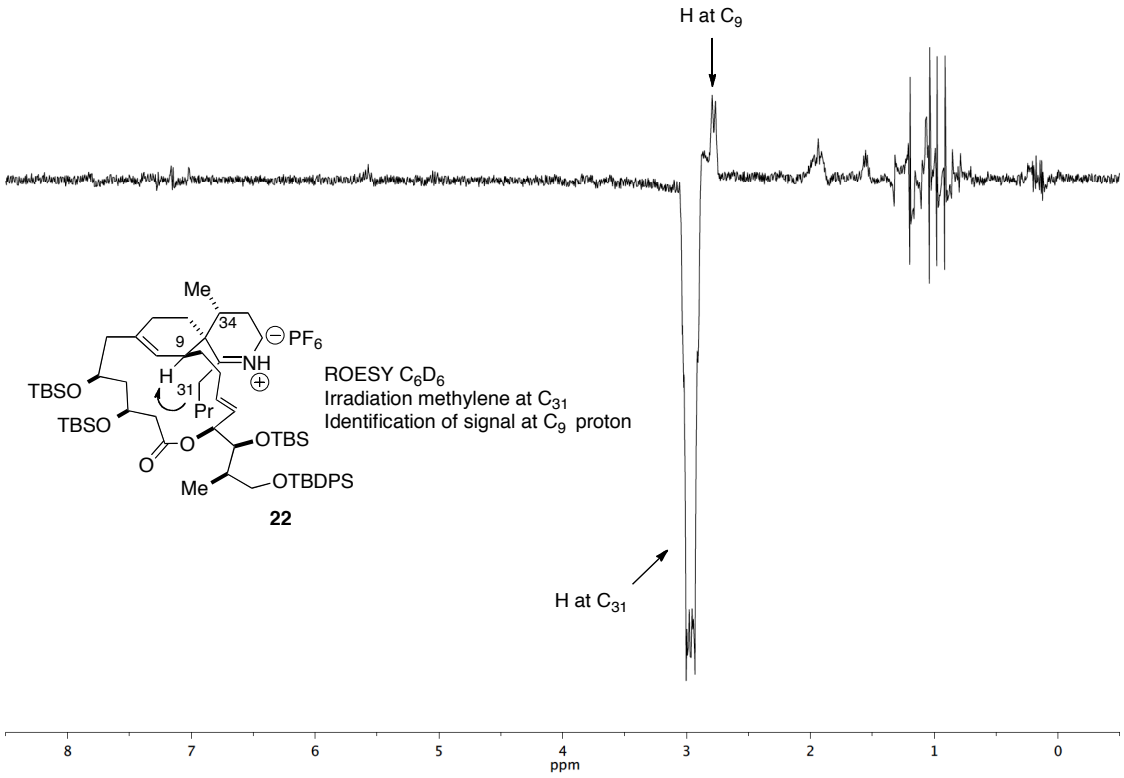

ROESY $C_6D_6$
Irradiation of $C_{34}$ Methyl
Signal at $C_9$ Proton

**12**

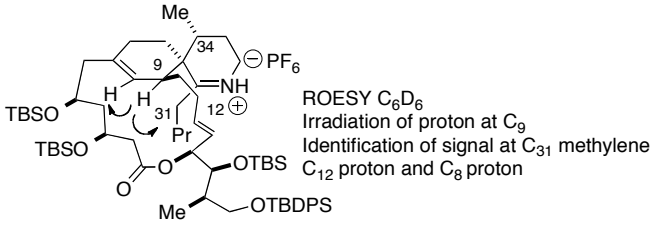



Me
34
PF6
NH
8
H
H
9
Pr
TBSO
TBSO
O
OTBS
O
Me
OTBDPS
22
TOCSY C6D6
Irradiation of proton at C8
Identification of signal at C9 proton
H at C8
H at C9
8
7
6
5
4
3
2
1
ppm

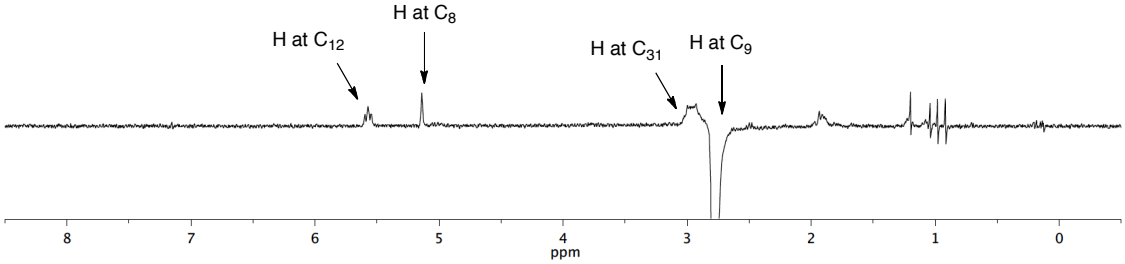

Me
34
PF6
NH
31
Pr
TBSO
TBSO
O
OTBS
O
Me
OTBDPS
22
TOCSY C6D6
Irradiation methyl on butyl group (C28)
Identification of signal at C31 proton
alpha to iminium
H at C29
H at C31
8
7
6
5
4
3
2
1
0
ppm

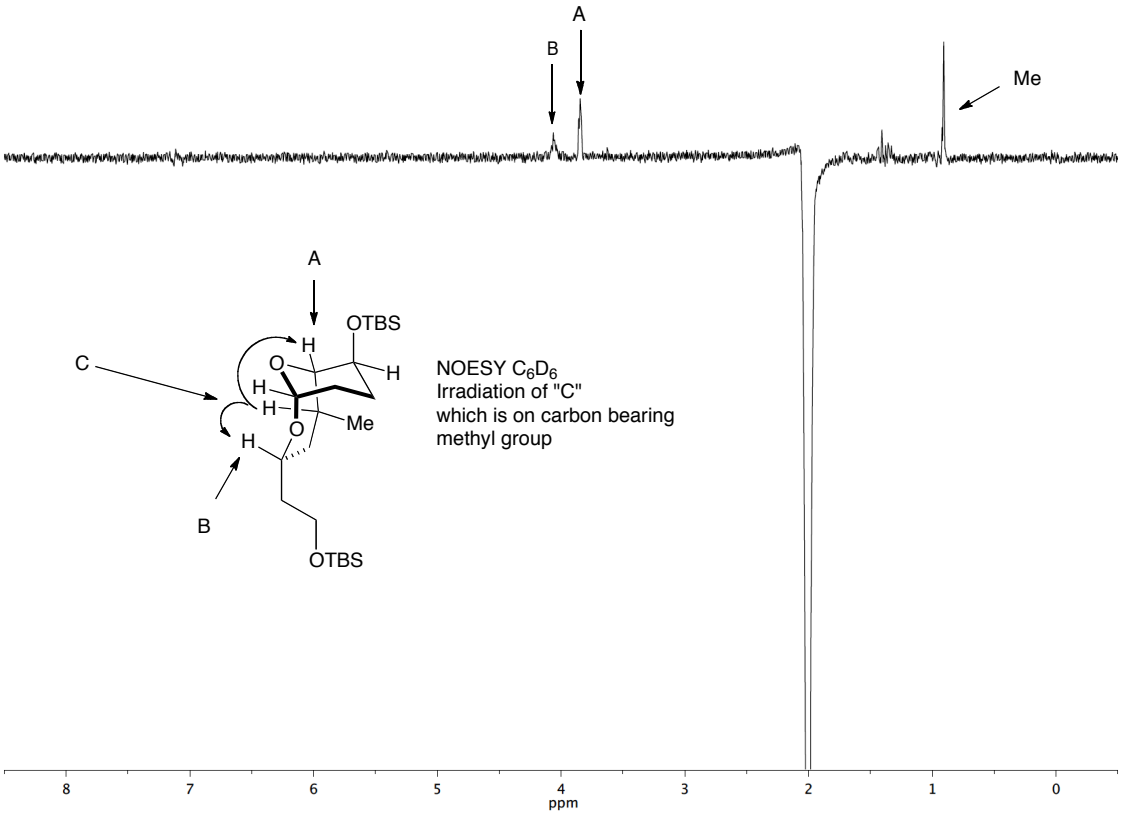

H at $C_9$
H at $C_{31}$
Me
34
9
$PF_6$
NH
H
31
Pr
TBSO
TBSO
O
O
OTBS
Me
OTBDPS
ROESY $C_6D_6$
Irradiation methylene at $C_{31}$
Identification of signal at $C_9$ proton
8
7
6
5
4
3
2
1
0
ppm

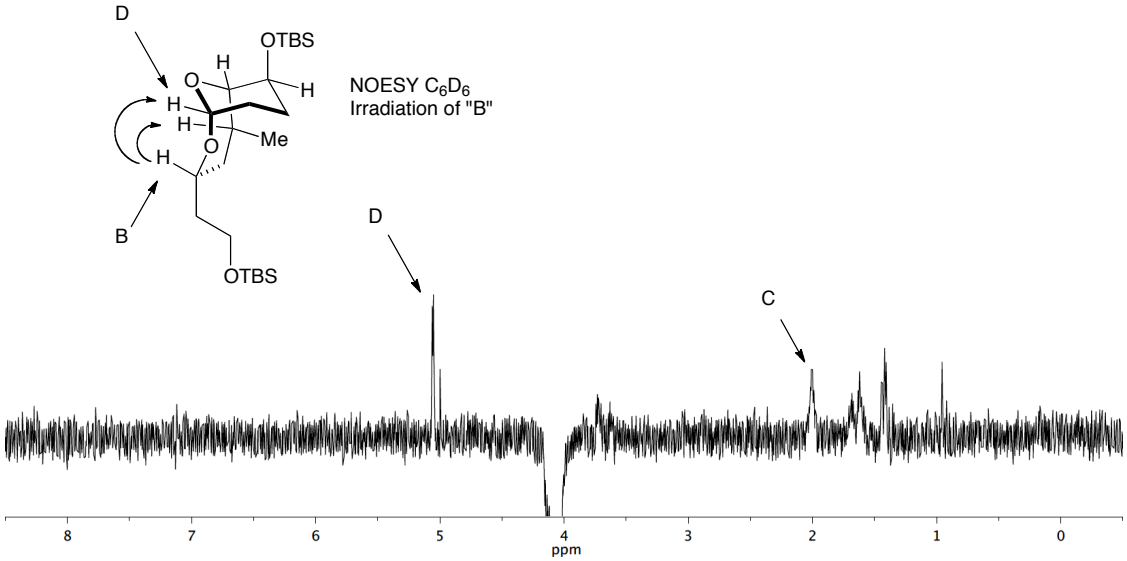
**22**

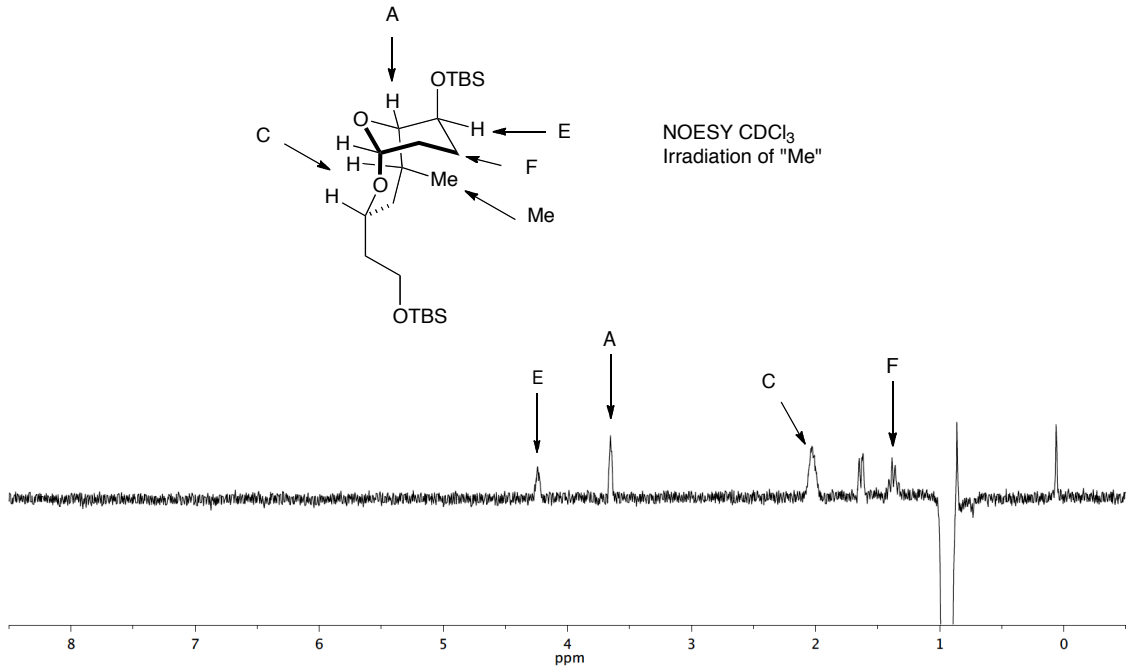

Me
34
9
$PF_6$
NH
12
H
H
31
Pr
TBSO
TBSO
O
O
OTBS
Me
OTBDPS
ROESY $C_6D_6$
Irradiation of proton at $C_9$
Identification of signal at $C_{31}$ methylene
$C_{12}$ proton and $C_8$ proton

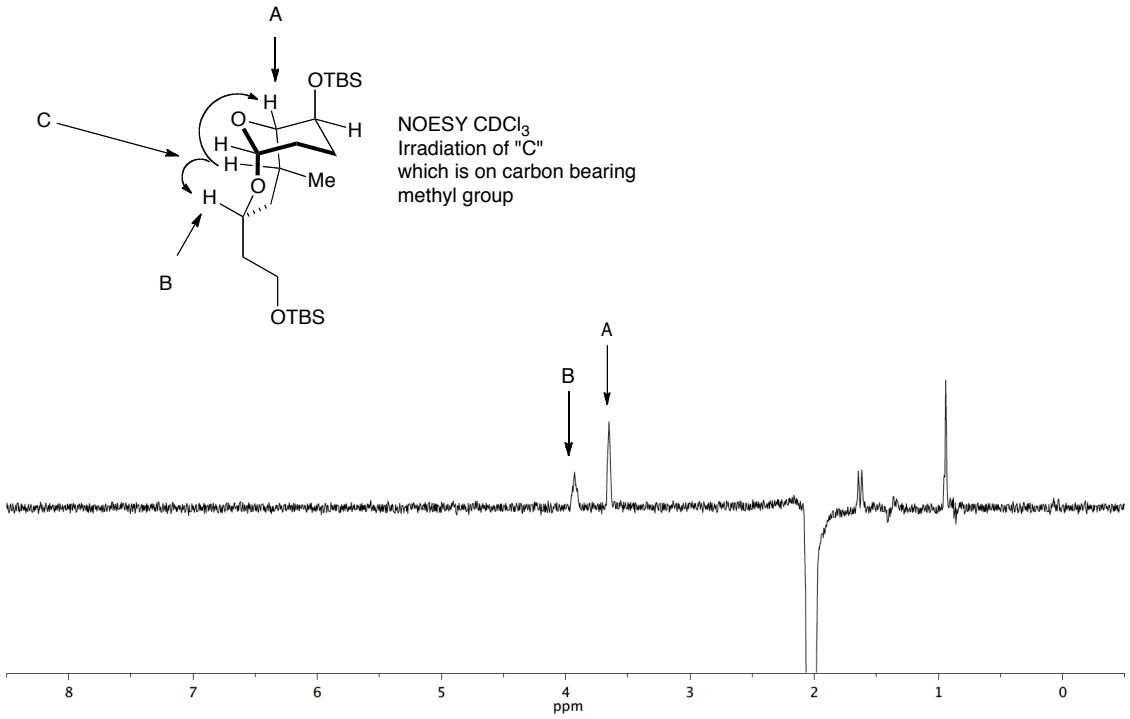
**22**


H at $C_{12}$
H at $C_8$
H at $C_{31}$
H at $C_9$
8
7
6
5
4
3
2
1
0
ppm


A
B
Me
A
OTBS
C
H
O
H
H
H
O
Me
H
B
OTBS
NOESY $C_6D_6$
Irradiation of "C"
which is on carbon bearing
methyl group
8
7
6
5
4
ppm
3
2
1
0


D
OTBS
H
O
H
H
H
O
Me
H
B
OTBS
NOESY $C_6D_6$
Irradiation of "B"
D
C
8
7
6
5
4
ppm
3
2
1
0


A
OTBS
H
O
H
E
C
H
H
F
Me
O
H
Me
OTBS
NOESY CDCl3
Irradiation of "Me"
A
E
C
F
8
7
6
5
4
3
2
1
0
ppm


A
OTBS
C
H
O
H
H
H
Me
O
H
B
OTBS
NOESY CDCl3
Irradiation of "C"
which is on carbon bearing
methyl group
A
B
8
7
6
5
4
3
2
1
0
ppm